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[*May* 10, 1955]

PSYCHOLOGICAL FACTORS IN EDUCATIONAL DISABILITY

Dr. D. Russell Davis and Dr. Norma Kent[1] (Psychological Laboratory, University of Cambridge):

Intellectual Development in School-children, with Special Reference to Family Background
[Abridged]

The most satisfactory evidence on the effects of different kinds of home on intellectual development would be found in the comparison of monozygotic twins brought up in different environments. Since their genetical constitutions are identical, any differences in their mental development could be attributed to environmental factors. But the number of pairs of identical twins available for study is small, especially cases in which the two members of a pair have been brought up in environments differing in an easily defined way. So far therefore the evidence from this source is scanty.

The study of children removed from their natural parents at various ages and put into foster homes has been a more profitable source of evidence. In researches of this kind the effects due to inheritance can be estimated independently of those due to environment, at least to some degree, for correlations with the natural parents can be taken as measures of the effects of inheritance, and the correlations with the foster parents as measures of the effects of environment. The rate of intellectual development has been shown in this way to depend upon various qualities of the foster home. Thus intellectual development is favoured when the foster parents are of superior intelligence, education or occupation. But the correlation coefficients between the children's IQs and these factors tend to be relatively low; coefficients of the order of 0·3 have usually been reported when the children have been fostered within the first few months of life. Several attempts have been made to identify factors of similar or greater importance. Skodak (1939), notably, has had some success in this. She prepared a "Home Inventory", which was designed to assess what may be called the *stimulation value* of the home. This inventory is a curious mixture of items, for it includes, amongst other things, ratings of the availability of toys, and their stimulation value, the provision of space for play, the participation of parents in the children's play, the frequency of play with other children and the quality of the conversation and of the reading matter in the home. The assessments of the foster homes on this inventory correlated more highly with the children's IQs than did the IQs or the educational or occupational levels of the foster parents, the coefficients in some samples being as high as 0·49 at the older pre-school ages. Studies of fostered children, however, have not yet been pushed far along these lines. One reason for this has been the lack of adequate methods of assessing other than limited aspects of the home. The aspects which are the most easily defined and measured are not necessarily the most influential. This methodological problem besets all kinds of research in this field.

A further point of interest arises from studies of fostered children. The correlations between the children and their natural parents, and between the children and their foster parents, vary in closeness according to the age at which the children have been moved from one home to the other. The coefficients for the correlations with the natural parents are hardly above zero if the children have been moved within the first few months of life. The later they have been moved, the larger are the coefficients for correlations with natural parents, and the smaller remain those for correlations with the foster parents. From these and other similar findings one may argue that the rate of intellectual development is set

[1]In receipt of a personal grant from the Medical Research Council.

not at birth but only gradually during the first few years of life. The results of some recent investigations on the growth of intelligence in children living in their natural homes point to a similar conclusion. The coefficients of correlation between tests and retests vary in size according to the age at which the children are tested and the interval between test and retest. The trend of the variations is interesting. The coefficients tend to be relatively high during the school years; that is to say, IQs tend to be relatively constant during these years. They are much less constant at younger ages. The major part of the increase in constancy occurs between 2 and 5 years old (Honzig *et al.*, 1948). It is, therefore, especially among the children's circumstances during these years and earlier that one should look for some of the factors which determine IQs subsequently.

What are the responsible factors? Bowlby (1951) has drawn attention to the importance of the mother-child relationship, and to the effects of disturbances of the mother-child relationship in producing intellectual retardation as well as mental ill-health. Many American investigations on fostered children have concentrated on the stimulation value of the home. Levy (1933, 1943), on the other hand, has studied the effects of what he calls "maternal overprotection" on progress in various school subjects as well as on personality, and has found that overprotected children tend to read well, but to do less well in arithmetic. The effects of position in the sibship are also relevant, and in researches which involve the comparison of the intelligence or attainment of children occupying different positions in order of birth, many of the genetical factors are controlled. Only children and children first and last in order of birth seem to occupy a favourable position. However, it is debatable what advantages these positions give, to which the children owe their intellectual prowess.

Our approach is largely from the standpoint of theories of learning (Davis, 1954*a*, *b*). Hence arises our interest in what we call the management and discipline of the home. The term discipline, which we use in a broad sense, means the methods of training adopted by the parents, both father and mother, and especially their use of reward and punishment, the frequency, consistency and generosity of rewards, the degree of stimulation, the degree of interest taken in the child's progress and the standards of achievement expected. Variables of these kinds are not easily assessed reliably, but they are meaningful aspects of the circumstances in which the children are brought up. We depend for their assessment on leisurely and often lengthy interviewing usually of the mother or mother substitute. The interviews are retrospective and are designed to discover the kind of discipline adopted by the parents in bringing up the particular child under consideration. Our preference of interviews to questionnaires is deliberate.

For the purposes of our researches each child is put, on the basis of the information elicited at the interview with his mother, into one of four arbitrarily defined classes according to the kind of discipline to which he has been mainly subjected. These classes we call: *demanding*, *overanxious*, *unconcerned* and *normal* (Kent, 1954). We look then for relationships between the classes of discipline and the results of intelligence and other tests. That is to say, we look for relationships between external conditions and behaviour variables, and in this way we devote ourselves to finding answers to the traditional question of experimental psychology: under what external conditions does a given activity or phenomenon occur? (Bartlett, 1932). In the same tradition we regard the class of discipline as the independent variable, and the test results as dependent variables. This feature of our work is in contrast to many of the psychological researches carried out recently in this country, for instance, at the National and Maudsley Hospitals, which have been concerned, without reference to external circumstances, with correlations between two or more tests made on the same individuals. Researches of this kind have certain advantages in method and convenience, but, because they neglect external variables, the interpretation of their results has, in our opinion, tended to attach undue importance to organic and constitutional factors.

Our subjects have been samples of 8-year-old children drawn from primary schools in Cambridge. We have had to forgo the methodological advantage of direct control of genetical factors, because sufficient examples of identical twins or of children fostered early in life have not been available to us. We have had to enquire, therefore, whether our results might be due to the disguised effects of physical inheritance rather than to the effects of environment on mental development, and to test this alternative hypothesis whenever possible. However, we have concluded in every case that the environmental hypothesis is the more reasonable, although we cannot definitely exclude the genetical hypothesis.

The choice of 8-year-old children as subjects is a compromise. It would be easier to obtain information from the mothers of younger children about the discipline during the important years, but on the other hand IQs are fairly constant at this age. Also we are especially interested in the effects of the various disciplines on the development of verbal and academic abilities; at a mental age of 8 and above the Binet Scale provides measures of

these abilities mainly. For the measurement of practical abilities we have relied on the "performance" sub-tests of the Wechsler Intelligence Scale for Children.

We shall now report summarily the results of an investigation on 118 school children. Three tests were applied: the Revised Stanford Binet (Form M), the "performance" sub-tests of the WISC and Schonell's Graded Word Vocabulary test.

Let us first consider the characteristics of the children from *demanding* homes by comparing their test results with those of the children from *normal* homes. Typically, *demanding* parents set high standards for their child, and they reward ungenerously. They provide opportunities for him to learn, but expect him to conform to an inflexible model of what they think he should be. In particular, they expect him to do well at school. *Normal* parents are more tolerant, and their standards, although positive, are reasonably related to the child's needs, abilities, and spontaneous interests.

The mean IQ of the children from *demanding* homes on the Binet Scale was much higher (124 compared with 110 normal). Their mean IQ on the WISC sub-tests was only slightly and not significantly higher. They did rather better, although not significantly better on the reading test. These results show that verbal abilities tend to be well developed in children from *demanding* homes relative both to practical abilities and to the verbal abilities of children from normal homes. 12 of the 118 children in the sample had IQs of 140 and above on the Binet Scale; 9 of these had been subjected to a *demanding* discipline. These children pay a certain price for their intellectual prowess.

There were several children in the *demanding* class whose Binet IQs were above average, but whose reading age was three or more years less than their mental age. This is the association of scores which has excited so much comment from neurologists. These children had met difficulties in their reading at the age of 5 or 6 years, the main sources of which, it seemed to us, lay in such things as faulty methods of teaching (especially in small private schools), irregular attendance at school, because of illness, or several changes of school, or a combination of these factors. These difficulties being aggravated by excessive demands by their parents, reading had acquired an exaggerated importance, failures had been magnified, and unfavourable attitudes towards reading induced.

The salient feature of the children from *overanxious* homes was their poor score on the "performance" tests, in which their mean IQ was significantly lower than the mean IQ in the normal class (101 compared with 110). On the Binet Scale and on the reading test, their means did not differ from those in the normal class.

Their parents have sapped their confidence and restricted their activities for fear of what might happen to them. *Overanxious* parents are ceaselessly anxious lest their child should fall short of what they expect, and what they feel others, such as relatives, expect, and their model is inconstant, although it may be emphatic.

The number of children in the *unconcerned* class was too small to be able to draw definite conclusions. *Unconcerned* parents tend to be indifferent to their child's successes and failures, and their interest in him is weak and negative. Their discipline tends to be inadequate, haphazard and inconsistent. The children of *unconcerned* parents did poorly on all three tests, and especially so on the Binet Scale and on the reading test, on which their reading age was significantly lower than that for the normal class (6·4 compared with 8·4). In the *unconcerned* class, verbal abilities were on the whole less well developed than were practical abilities.

These results seem to show that intellectual development as measured by standard intelligence tests is influenced to a substantial degree by the discipline provided in the home. They are in keeping with the general trend of contemporary opinion on the importance of environmental factors in determining IQs, and in combination with the results of other investigations, they suggest that the traditional views which attach overriding importance to genetical factors should be revised. It seems reasonable to hope that further study of the effects of various unfavourable disciplines, with attention to the age of the child at the time of their impact, will throw new light on the ætiology of the mental defects.

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Mr. R. Lynn (Psychological Laboratory, University of Cambridge):

Personality Factors in Reading Achievement

In this paper I wish to present the results of an investigation into the effects of anxiety upon the reading achievement of school children. Because of its intimate association with neurosis, anxiety is sometimes assumed by clinicians to be necessarily incapacitating and inimical to worldly achievement. It is probably fair to say that most educational psychologists have adopted this view. Thus Schonell (1942) advises the educational psychologist investigating causes of backwardness to look for anxieties and conflicts. Kanner (1935) states that

"There are children so anxious for success that their very anxiety has an inhibiting effect on learning."

On the other hand, a smaller number of writers have held the opposite opinion that anxiety may actually contribute to academic attainment. Among those who have taken this view are such distinguished writers as Sir Cyril Burt and Mrs. Melanie Klein. Speaking of anxieties in children, Burt (1937) writes:

"These, however, are less likely to retard school progress; on the contrary, they often prove a source of extra effort and even overwork."

And in her own very different field and language, Melanie Klein (1952) maintains a similar position in her description of intellectual development as a defence against anxiety. The present research was undertaken to see whether any support could be found for these views by an examination of normal school children.

The Tests and the Subjects

80 children attending a junior school in Cambridge were selected by the headmaster as being good, poor or average readers. Their ages ranged from 7·5 to 11 years; there were 42 boys and 38 girls. The children were tested and interviewed individually for some three hours over four sessions of about three-quarters of an hour each, and were given a wide variety of intelligence, scholastic and personality tests.

Their reading age was assessed by Schonell's Graded Reading test (using the norms as modified by Vernon (1950)), and each child was given a score of reading attainment by subtracting the chronological age from the reading age. Thus a child of 10 years with a reading age of 11, was given a reading attainment score of +12 months.

Of the many methods psychologists have evolved for assessing anxiety, this paper is concerned only with the results of direct questions, although the findings have been, in general, confirmed by several objective and projective tests. The term anxiety is used in the sense described by Freud (1936) in his later discussions, i.e. as a feeling of apprehension following upon the loss, or the threat of loss, of the presence of the mother, of her love and approval, and of the approval of society. There was no attempt to measure castration anxieties. Anxiety was assessed by asking the children the following six questions, one mark being scored for each affirmation, or half a mark where the answer was equivocal.

(1) Have you ever been frightened by the thought that your mother might die?
(2) Are you upset if your mother goes out in the evenings?
(3) If you have been away from your mother at any time, have you felt unhappy?
(4) When you are reading or making things in the evening, do you dislike being alone?
(5) Does scolding make you feel upset?
(6) Are your feelings easily hurt?

These questions were asked towards the end of the interview, when a friendly relationship had been established between the child and the writer. They were asked informally, as if they had arisen by chance in the course of conversation. This method was chosen because it allowed an objective and quantitative method of scoring such as would not have been possible if the children had been assessed clinically. The questions were put informally because it was felt that the children would be more likely to answer them sincerely than if they had been presented as a formal questionnaire. Further, all the testing was carried out in the school, where the surroundings and the tester were already familiar. These circumstances probably encouraged the children to give frank answers to the questions; on the whole, they showed surprisingly little embarrassment, and gave every appearance of answering the questions truthfully.

As a control for these personal anxieties, the following series of questions concerning impersonal anxieties was also given:

(1) Are you afraid of any sort of animal?
(2) Are you afraid of thunder?
(3) Do you often feel nervous?
(4) Do you often have frightening nightmares?
(5) Are you afraid of the dark?
(6) Do you ever feel worried when there is nothing to do?

Results

On the whole the scores on both tests of anxiety were low; the mean score of personal anxieties was 1·26; of impersonal anxieties, 1·56. When these scores were correlated with those of the reading test, there appeared a positive correlation of +0·33 between reading attainment and the personal anxieties, and a correlation of +0·24 between the reading attainment and the impersonal anxieties. Both these correlations are significantly different from zero at the 5% level, although they are not significantly different from each other.

In general, these results confirmed the writer's clinical impression. A brief description of one girl will perhaps illustrate some of the features of the anxious good reader. This girl was exceptionally good academically; she was 10·4 years old at the time of testing, and achieved a reading age of 16·4. She was the youngest girl in the top class and had received special permission to take the grammar school selection examination a year early. Her Binet IQ was 146, although her Wechsler (WISC) performance IQ was only 115. On the personal anxieties she scored 4, and on the impersonal anxieties 3. A visit to her home revealed that it was substantially broken; the father worked in a town 15 miles away, and only came home once a month. The mother was a very timid woman, rather typical of the overprotective anxious mothers of nervous children described in the psychiatric literature (Levy, 1943). She described how the girl had a "mania" for tidiness—an interesting example of the compulsive features often associated with gifted children and adults—and how she spent all her evenings either reading or playing lexicon patience, a word-spelling game. It is not surprising that she does so well at school.

The association of anxiety and reading ability admitted one or two exceptions, children with some anxiety who were poor at reading. There are not enough of these to have any statistical significance and they may be due to chance factors. Taking the evidence of the intelligence tests into account, however, the writer believes that the present sample provides some cases which support the common belief that anxieties may prove inhibiting to school work, although these cases seem to be a minority.

Discussion

The investigation shows that reading achievement is associated with anxieties in general, and especially with anxieties about the mother's presence and approval, and the approval of society. The finding that anxieties and attainments are related might perhaps be explained by the supposition that there is a common factor underlying both; and such a common factor is not difficult to find, for anxieties and reading are both *learned*, and their association might simply be due to the fact that some children learn more easily than others. A child with an efficient nervous system might be expected to learn both to read and to fear with equal facility.

Alternatively, there may be some common environmental circumstance which would account for the relationship between reading and anxiety. It seems likely that such an environmental factor may be present in the types of mother which Dr. Russell Davis and Dr. Kent (1955) have called "demanding" and "overanxious"; they have shown that these mothers tend to have children who are good readers, and it is well known that anxious children also frequently have mothers of this type (e.g. Banister and Ravden, 1944).

It looks as if only some explanation in terms of a common factor can explain the association of impersonal anxieties and reading achievement, since it is difficult to see how either could have any direct effect on the other, for example, how being frightened of an animal could directly affect a child's reading ability. That this is not the only explanation, however, is suggested by the higher correlation between reading and anxieties about personal relationships. Here it is more plausible that anxiety could have a direct effect on the reading achievement. This may be described in psychoanalytic terms as the building up of a defence mechanism against anxiety, or in learning theory terms as a high degree of reinforcement due to anxiety reduction.

It may be, therefore, that too little anxiety is just as undesirable as too much. This view is supported by Bowlby's (1951) account of the affectionless character, who has so little concern about the opinion of society that the usual deterrents of disapproval mean nothing to him. If this view is correct we should think more in terms of redirecting anxiety than of trying to eliminate it altogether.

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Mr. G. Ettlinger and Mr. C. V. Jackson (Psychological Department, The National Hospital, London):

Organic Factors in Developmental Dyslexia [Abridged]

The incidence of certain physical factors in cases of the reading disability commonly designated as *specific* or *developmental dyslexia* is noticeably greater than in a randomly selected group of individuals. These factors include anomalies of lateral preference, in particular left-handedness and "crossed" eye-hand preference (Orton, 1937; MacMeeken, 1939); anomalies in the visual perception of apparent movement, considered by some authors to indicate failure to establish normal hemisphere dominance (McFie, 1952); minor EEG abnormalities, occasionally associated with a history of brain injury or even frank epilepsy (Spiel, 1953; Faust, 1954); anomalies of intellectual maturation, especially with regard to spatial and temporal analysis (Ajuriaguerra, 1951); and last, but not least, indications of a specific genetical background (Hallgren, 1950). This paper reviews some recent studies of dyslexia in which organic factors have been outstanding and presents a small group of cases we have recently studied at the National Hospital, Queen Square.

Our studies have their origin in McFie's work on developmental dyslexia employing the Jasper-Raney test of cerebral dominance. In this test, the two half-fields of vision are compared for sensibility to apparent visual movement and the hemisphere implicated as dominant is normally found to be the same as that predicted on the basis of handedness. McFie compared the findings on this test in a group of 12 cases of developmental dyslexia and a group of 12 normal subjects without reading disability. The results suggested that dyslexic subjects perceive apparent movement poorly and often show no clear-cut directional predominances. McFie was therefore led to conclude that in these cases "the neurophysiological organization corresponding to dominance has not been normally established in either hemisphere".

Spiel (1953) investigated a family in which the father, his three brothers and his two sons had selective difficulties in reading. Neurological examination of the two boys proved negative. However, both their EEG records showed poor development of the parieto-occipital alpha rhythm, but without evidence of focal lesion.

These findings of McFie and Spiel are complementary in so far as both indicate some maturational defect in the posterior regions of the brain. It is noteworthy that unusual or "borderline" features were reported also in the EEG records of 4 out of 6 of McFie's cases. A combination of neurological defects with specific reading disability has also been reported by Bach (1949) and Faust (1954) and the whole matter has been discussed by Hoff *et al.* (1954).

Genetical considerations in specific dyslexia have been reviewed by Hallgren (1950) in a valuable study. Although this author was unable to differentiate between hereditary and secondary dyslexia on clinical grounds alone, he reports a high incidence (i.e. 88%) of families in which the relatives of his actual cases were similarly handicapped by dyslexia.

Some further evidence that consistent anomalies of performance occur in specific dyslexia has recently been adduced by Ajuriaguerra and his co-workers (Ajuriaguerra, 1951; Galifret-Granjon *et al.*, 1953). In particular, defects in the establishment of right-left orientation, spatial judgment and temporal organization were marked in a significant proportion of their cases. These results are of particular value in so far as they suggest that dyslexia is not an isolated deficit but one facet of a more generalized defect of intellectual maturation.

We have been able to confirm many of these organic features in a series of cases referred to the Psychological Department of the National Hospital. The histories and test results in respect of 24 patients recorded as presenting selective reading defects were reviewed. This group does not overlap with that studied by McFie (1952). It was, however, decided to exclude 16 cases on account of insufficiently pronounced dyslexia (4 cases); the presence of marked emotional or psychoneurotic features (5 cases); and incidence of frank neurological disorder which could be construed as primary to the dyslexia (7 cases). Although

The resulting group of 8 cases is far too small to permit general conclusions to be drawn, it was thought preferable to exclude all patients whose reading disability could be at all plausibly related to some associated factor, neurological or psychogenic.

The *final case material* consists of 5 boys and 3 girls, with ages varying from 7 to 12½ years at the time of our examination (Table I). In every instance mental age exceeds

TABLE I

	Chronological age		Intelligence (Terman-Merrill M.A.)		Reading age (Burt)	Visuo-constructional tests (Kohs M.A.)
	Years	Months	Years	Months	Years	Years
Case (1)	8	11	12	0	7	8
(2)	10	0	10 or better	0	5½	11
(3)	12	5	13 or better	2	8	—
(4)	10	6	11 or better	0	6½	—
(5)	11	6	11 or better	10	8½	8½
(6)	7	1	7	6	5	6½
(7)	9	1	IQ 116		7	9½
(8)	10	0	10	0	6	7½

chronological age (thus excluding general mental defect) and the average amount of selective reading retardation by comparison with each child's mental age is four years (minimum two and a half years). It was found that all 8 children were comparably backward on Burt's Oral Spelling Test but only one was selectively retarded on tests of mental arithmetic. The nature of the reading and spelling errors broadly conforms in every instance to the characteristic pattern found in selective dyslexia.

Neurological examination was negative in all cases. There was, however, a history of early head injury in one case and of meningitis following mumps in a second. One patient gave a history of infrequent epileptic attacks (2 major and 7 focal fits involving the left hand). No evidence of neurological disorder was present in the remaining 5 cases.

On *psychological examination*, 3 children (out of 6 tested) gave evidence of *selective impairment on visuo-constructive tests*. The tests used were the Kohs Blocks and the Terman-Merrill "Memory for Designs" subtest, and our criterion of selective impairment was a deviation of two years or more from the mental age established on the full Terman-Merrill scale. It was interesting to note that although 2 of the children affected on these tests were below the age of 10, the third was aged about 12 and might therefore be expected to present a lesser degree of retardation. None the less her M.A. on the Kohs full scale was three and a half years below that derived from the Terman-Merrill. Although these results are obviously insufficient to permit any conclusions to be drawn, they broadly support the findings of Ajuriaguerra and his co-workers in so far as they go.

Certain features connected with *lateral preferences* deserve especial mention (Table II).

TABLE II

	Neurol. signs	Handedness		Cross laterality	Jasper-Raney test
		Personal	Familial		
Case (1)	None	R	Father partly L-handed	None	Indefinite dominance
(2)	None	R	Father partly L-handed: and L-footed	Eye-hand	Indefinite dominance
(3)	None	R. from age 7 onwards	Not known	Eye-hand	—
(4)	None	L	Father L-handed	Foot-hand	Indefinite dominance
(5)	None	R. from age 5 onwards	Uncle L-handed. Mother not fully R-handed	Not known	—
(6)	Sl. L-hand weakness	R	All R-handed	Not known	—
(7)	None	R	Not known	None	—
(8)	None	Ambidext: R>L	Mother partly L-handed	Foot-hand	R-dominant

4 out of 8 cases were fully right-handed and one fully left-handed. Two cases although right-handed when examined had originally preferred their left hand up to a relatively

late age. One case was predominantly right-handed but partly ambidextrous and certainly left-footed. There are thus signs of left or mixed handedness in half of this small group of cases. It was also notable that one of the fully right-handed children was left-eye dominant, the partly ambidextrous child was also left-eye dominant, and that the fully left-handed child was right-footed. Indeed consistent unilateral hand, foot, and eye preferences were present in only 2 of the 6 cases for whom this information is available.

Parental handedness could be established for 6 cases. Among the 4 fully right-handed children, there was evidence of a left-handed father in 2. In the case of one of the shifted sinistrals, 2 paternal uncles were reported to be left-handed or eyed and the mother was not fully right-handed. The maternal grandfather had two left-handed brothers. The mother of the ambidextrous boy was partly left-handed and the father of the fully left-handed boy was likewise fully left-handed. There is thus some sinistral ancestry in 5 out of 6 cases in which relevant data are available.

A *familial history of dyslexia* was elicited in only one case. This was in a girl who was left-handed up to the age of 5 and then shifted to the right hand. She had sinistral antecedents on both sides of the family, and some evidence of reading-spelling disability in the maternal grandfather.

On the *Jasper-Raney test of lateral dominance*, results were obtained in 4 cases. 2 fully right-handed cases gave results of the type adduced by McFie (1952) as indicative of indefinite cerebral dominance, as did also the fully left-handed child. The ambidextrous but left-footed boy saw movement to the left, probably indicating right occipital lobe dominance.

EEG records are available in 2 cases. In one (the girl with epilepsy) the record gave evidence of a focus in the right Rolandic area. In the other—the girl with shifted handedness and dyslexic antecedents—the EEG indicated marked, though not definitely pathological, asymmetry of the alpha rhythm, which was larger and more constantly present on the right, more especially in the parietal region.

These findings, although very fragmentary, find confirmation in a number of large-scale studies. Thus the exceptionally high incidence of left-handedness in dyslexics has aroused comment on the part of many workers, of whom some (e.g. Ajuriaguerra, 1951) are inclined to link it ætiologically, at least in certain instances, with the reading disability. "Cross-laterality," again, has been adduced as a causal factor in dyslexia by a number of workers, in particular McMeeken (1939), though Hallgren (1950) has failed to substantiate her findings.

Our very limited results tend in general to confirm McFie's findings and to support his claim that, in many dyslexics at least, normal dominance has not become fully established in either hemisphere. Although acquired factors, such as early brain injury, may play a part in this, it is more probably due in the majority of cases to some hereditary factor governing cortical maturation of function and the proper establishment of cerebral dominance. At all events, reading defects of the kind presented in these cases cannot properly be attributed to environmental or psychogenic influences. The frequent incidence of anomalies in lateral preference—both personal and familial—of crossed laterality, of equivocal findings on the Jasper-Raney test, and of defects in spatial and temporal perception render it virtually certain that developmental dyslexia is of constitutional origin. On our view, it is best regarded as a selective failure of learning directly due to defective maturation of those cerebral mechanisms underlying the visual aspects of language.

We should like to acknowledge the help and advice generously given to us by Professor O. L. Zangwill.

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Section of Epidemiology and Preventive Medicine

President—Professor A. BRADFORD HILL, C.B.E., D.Sc., Ph.D., F.R.S.

[*April* 15, 1955]

Changing Concepts in the Control of Tuberculosis in the United States

By IRA HISCOCK, Sc.D.

Professor of Public Health, Yale University, and President-elect, American Public Health Association

SCIENCE and the society in which it functions are closely interrelated. The application of science to medicine and public health has eased suffering, prolonged life and affected the age distribution. Chronic diseases are a consequence of the debilitations of the ageing process. The death-rate of one of the chronic communicable diseases, with characteristics of relapse, and formerly the greatest killer, has dropped sharply; but the morbidity rate continues high. A review of milestones in progress[1] suggests key points of an accelerated attack on tuberculosis. Meanwhile, the search for new knowledge must continue, while we use what we do know more intensively and more effectively.

The picture of the disease tuberculosis has changed greatly from the administrative, the economic, the epidemiological, the clinical, the social and the treatment standpoints. Many have a mixture of sadness and satisfaction in contemplating the closing of the Trudeau Sanatorium at Saranac Lake. Associated with the sadness is a belief that this does not mean yet that private sanatoria are no longer needed nor that public sanatoria can be converted wholesale to the care of other chronic illnesses, including mental diseases. The satisfaction is related to a recognition that this disease is "on the run", and that countless lives are being saved. Newer methods of treatment, including chemotherapy and surgery, coupled with more vigorous measures for early diagnosis, for rehabilitation, and for the education of the public, are paying priceless dividends.

The whole machinery of control was thrown out of balance by these remarkable strides, and a great new opportunity appeared. There are social implications. Furthermore, every community needs to evaluate anew the parts of its problem and its programme.

The approach involves epidemiology and statistics (utilization of A. Bradford Hill's "Clinical Trial" studies, for example; *see* Hill, 1951, 1952), with better "source case" finding, health education of the patient, the public, and the profession, coupled with rehabilitation and a set-up to help build up the person with the disease. More use could be made of the tuberculin test, in a "mop-up campaign", particularly in large eastern urban areas.

The present situation is reflected in the following summary:

(1) There are some 400,000 active cases, or 250 per 100,000 in the United States. Tuberculosis ranks 11th as a major cause of death.

(2) Recently, the decline in the number of tuberculosis deaths has been much more rapid than the decline in the number of newly reported cases of active tuberculosis. Noteworthy is the fact also that at least 5,000 cases were reported for the first time on death certificates in 1952. Also, total new reported active cases then numbered 85,600 with 24,621 deaths from tuberculosis.

(3) The rate of death is higher in each successive adult age group.

(4) Tuberculosis death-rates and new case-rates are about twice as high for males as for females.

(5) Tuberculosis is expensive, and is far from conquered. The expenditures for tuberculosis in the United States by governmental and non-governmental agencies are estimated to be more than 600 million dollars a year.

(6) Income from the 1953 seal sale in the United States and possessions, according to the National Tuberculosis Association, was 23,889,044 dollars, or 14·8 cents *per capita*. There are some 3,000 tuberculosis associations in the United States to complement and otherwise help the governmental agencies in tuberculosis control measures.

(7) According to the Executive Director of the Trudeau-Saranac Institute: "Decline in the number of cases of tuberculosis in that segment of the population from which Trudeau

[1]From Koch's identification of the cause in 1882; Biggs' New York City resolution of the Board of Health providing for reporting of cases, free examination of sputum, and home visitation of "consumptives" in 1894; the 1908 International Tuberculosis Congress; to more recent X-ray and educational campaigns.

has drawn its patients is only one of the factors responsible for our closing. Probably of considerably greater importance are such factors as the excellent free care furnished by governmental institutions, the rising costs of private hospital care, the growth of home treatment of tuberculosis, the shortening length of stay in hospitals by new drugs and surgery, and the decreased incidence of disease relapse due to chemotherapy." (From a letter to Medical Director of the N.T.A.)

Changing Factors

Tuberculosis is spread chiefly from man to man. The pasteurization of milk and systematic measures to combat this disease in dairy herds have practically eliminated bovine tuberculosis in my lifetime. Dramatic accomplishments are recorded in the control of diseases due to an insanitary environment. Achievements are less easy with the contact-borne diseases because man is the focus for attention. His behaviour is influenced by attitudes and other factors less susceptible to control than his surroundings.

Numerous forces are responsible for the reduced mortality rates. The growing industrial cities of the U.S.A. had tuberculosis mortality rates of 400 to 100,000 habitants in the last century, dropping in the whole country to 200 by 1900 and to 100 by 1920; with an average rate now of under 20. Similar changes are recorded for Western Europe, Australia, and other areas (Winslow, 1951) besides those occurring also in many parts of the world where high tuberculosis death-rates still persist. Clinics and sanatoria were provided for the treatment of the disease in addition to conventional measures of isolation and quarantine. Improvements in social conditions included more adequate nutrition and improved health status for the whole population. Advances in community health resources since 1920 have been significant. But much remains to be done before the term "eradication" can be used.

Note on Treatment

Much has happened regarding treatment in eight years, but procedures are far from crystallized. Treatment of pulmonary tuberculosis was based on rest and support to the patient. Usually the patient reached an exercise level of four or more hours before discharge with medical approval. Pneumothorax was a common procedure, with a trend toward "primary thoracoplasties", while pneumoperitoneum became popular. Since the advent of antimicrobial drugs and the coincidental improvement in anæsthesia and pulmonary surgery, tuberculosis therapy has been in continuous change (Hedberg, 1955). Tuberculosis is a systemic disease that cannot be controlled by the excision or collapse of diseased parts alone. According to my clinical friends, the treatment of tuberculosis has not yet stabilized, except possibly in regard to the emphasis on long-term chemotherapy. Indications for resection are more conservative. While it is impossible to evaluate the results of treatment at this time, the reactivation rate after discharge is reported as decreased. In one institution, for example, before the advent of chemotherapy, the reactivation rate among patients discharged as well or improved was around 33%, over a five-year period. But, with the reduction of disability from physical immobilization, it is more difficult to convince the patient of the necessity for sanatorium treatment. Much time must be spent in the individual education of the patient regarding the problems of his disease as it relates to himself and to his family and community. This is of significance for everyone concerned with home care plans, including the institution, the community nursing and other health and welfare agencies, as well as for the family and the attending physician, With chemotherapy, it is possible to shorten the hospital stay for the intelligent and co-operative patient by a programme of post-sanatorium outpatient treatment with drugs, given under the supervision of the patient's private physician. The patient evidently needs, periodically, intensive laboratory studies, including the culture of gastric specimens.

Some are beginning to inquire why sanatorium care is necessary with present definitive treatment. Among the reasons two are important. (1) Patients with active tuberculosis are an actual or potential menace from the standpoint of public health, even with intensive drug treatment; (2) proof is lacking that drugs alone "cure" tuberculosis. Rest and support promote the patient's ability to heal his disease. Also, the toxic potentialities and the difficulty of taking some drugs can be mentioned. Meanwhile, the very young and the very old are two age groups seen more commonly in sanatoria than heretofore.

Tuberculosis Beds

In April 1954 there were 97,991 tuberculosis beds (federal and non-federal) occupied in 1,124 hospitals for the care of tuberculous patients with a rated capacity of 115,157 in the United States. In a year there was a decline in beds occupied of 2·2%, but there was an increase in federal beds occupied of 4·4%, with a decrease in non-federal beds occupied of between 3% and 4%. There were more than five times as many tuberculosis patients in tuberculosis hospitals as there were in other hospitals with tuberculosis units (U.S. Dept. of Health, 1954). We need to be cautious in the use of criteria for bed requirements for patients with tuberculosis.

What about cases?—In recent years the case-rates show that the incidence of tuberculosis in females is still high in early womanhood, but declines after 35, whereas in males the case-rate continues upward after 35. The State-wide reporting of new cases has declined much more gradually than the mortality rate. In the New Haven Hospital area of around 250,000 people, the cost of cases cared for in 5 State sanatoria in the one year of 1953 was some $520,000, suggesting that even in this community, with one of the lowest tuberculosis mortality rates (below 18), the disease is still prevalent. For another illustration, there were 192 more new cases reported in 1953 than in 1952 in California, but when weighed against the increase in population, the case-rate per 100,000 actually declined. The 1953 rate was 69·4 cases per 100,000, only a 2% decrease from 1952, and there was a total decrease of only 19·5% in the past five years. "So", as Merrill comments (1954), "despite the remarkable reduction in death-rate, the problem of tuberculosis is still with us, and it behooves us to improve our case-finding techniques. Case finding becomes even more important as newer treatments allow us to deal with cases more effectively. As cases become fewer and fewer, each one becomes relatively more significant in the spread of the disease."

What are key points of attack? In one large city in a recent year, 60% of the cases came from only three out of the total of census tracts. In another city, an overall positive tuberculin reaction of 5% was revealed among upper high school students. Is it wise to confine case-finding activities to those communities with high tuberculin rates? Selective case finding is a term with a meaning. In large cities, with a great admixture of population, how effective is tuberculin testing? For such cities, Merrill (1954) suggests that concentrated effort may best be directed to the census tracts of known high prevalence, the gaols, the hospitals, the clinics, and physicians' offices. In Los Angeles, the tuberculosis association set up a programme in the great county hospital which finds about one-tenth of the morbidity of the State.

Preliminary studies of the occurrence of tuberculosis in a transient, mobile population group of homeless men indicate a segment of the population requiring attention if the aim of a programme is to eradicate tuberculosis. This group is likely to take temporary jobs as food handlers—cooks, cooks' helpers, dishwashers, &c.—where opportunities to transmit the disease are common. In one group of over 400 studied, the rate of active new cases per 1,000 was 22·2, compared with the similar rate for a county mobile unit survey of the general population of 0·4 per 1,000, and 55½ times as high as the general rate in the large city for that year and 13·4 times as great as that found in a Men's Workhouse population—comparable as to composition and intensity of search (Jones *et al.*, 1954).

It is beyond the scope of this paper to consider in any detail many important and timely questions concerning BCG, tuberculin sensitivity, and experimental studies. While it is generally believed that "BCG vaccination does not take the place of other recognized methods of tuberculosis control . . . " WHO and many governments have accepted it as a useful public health measure, and as a result some hundred million persons have been vaccinated in a number of countries in recent years (*Bull. World Hlth Org.*, 1955; American Public Health Association, 1955).

In 1952 in the United States there were 24,621 deaths from tuberculosis, all forms, of which 2,135 were other forms than respiratory. The number of cases for the year is not known as precisely. Frequently the registers show from 5 to 9 cases reported per average annual death over a five-year period. Hence it is important to continue a systematic attack on the disease with emphasis on education and prevention, as well as on rehabilitation. In 7 States there is no so-called means test, and anyone can be cared for during the institutional period without individual cost to the patient and family. This has an important bearing on the ease of admission, on the length of stay, and on the freedom from financial anxiety associated with hospital bills. In Connecticut, for example, the means test is often a hardship. We try to teach that tuberculosis spreads by contact, and that one active case can infect many healthy people. Prevention depends on isolation, prompt treatment, and willingness of the patient to remain under treatment until he can go home without danger to himself and others. Simultaneously with other services, careful estimation of vocational abilities and needs and of supplying those needs is necessary. With the changes in length of stay, fewer and briefer rehabilitation services may be required.

The future.—There are indications that the case-rate for tuberculosis will not decline as rapidly as did the death-rate. In spite of the discovery of the causative agent years ago, there is still much to be learned about tuberculosis and its treatment. It is not known, for example, how many will relapse in the future with tubercle bacilli that may become resistant to drugs. Hospitalization during the infective stage, with proper public health education, will continue to be essential. Case-finding techniques need intensification, with emphasis on areas of high infection, and application of other selective processes. Treatment, education and rehabilitative services should be meshed as fully as possible. Divided responsibilities in the same community should be avoided.

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[*May* 17, 1955]

A Meeting Held at the London School of Hygiene and Tropical Medicine to Celebrate the Centenary of the Publication of John Snow's Classic Treatise "On The Mode of Communication of Cholera"

AN exhibition illustrating Snow's life and writings and the sanitary conditions of the time had been set up by the Department of Public Health of the London School of Hygiene and Tropical Medicine and was opened by the President of the Section on May 17. Amongst many other features this exhibition included illustrations of the episode of the Broad Street pump and of the classic investigation into the epidemic of 1855 in South London. Two copies of "On Cholera" signed by the author himself were on view together with a portrait of him believed to have been executed by a painter to the Court some time after Snow had administered chloroform to Queen Victoria at the birth of Prince Leopold in 1853. This portrait was lent by Miss Una Snow, a grand-niece of John Snow. With her permission it is reproduced (Fig. 1) together with a few illustrative items from the exhibition (Figs. 2, 3 and 4 are reproduced with the kind permission of the London County Council).

Two communications were presented to the Section: Snow—the Man and his Times by Professor J. M. Mackintosh, and Snow—an Appreciation by Professor Bradford Hill.

Snow—the Man and His Times

By J. M. MACKINTOSH, M.D., LL.D.

IN the sixth decade of the nineteenth century England presented a picture of noble prosperity. The Great Exhibition of 1851 was a triumph for the merchant. Ownership of land gave up its supremacy to expanding trade. The virtues of thrift and hard work fitted well into the prevailing morality of steadfast marriage and abundant family life. It is true that *Punch* and some other journals made fun of the Queen's fecundity, but she had the longest laugh by publicly approving the administration of chloroform by a relatively obscure physician called John Snow, at the birth of Prince Leopold. By 1852 Snow had taken up residence in a substantial house at 18, Sackville Street and has been described as a "fashionable" physician. Neither his income nor the attitude of his professional brethren supports this view. More probably he was regarded as a useful, but limited, *auxiliary* in anæsthetics. It is significant that he did not sign the bulletin announcing the birth of Prince Leopold or in 1857 of Princess Beatrice.

It is worth observing that Snow was not a member of Sir Benjamin Hall's Medical Council which failed to sweep back the incoming tide of cholera in 1854–55; and his views received scant and impatient attention from the official investigators.

To understand the reasons for this we must pay closer attention to the temper of the times. Much of England's prosperity was illusory and its morality superficial. The victories which had been won since the tawdry Regency were in clashes between one social class and its rival. The aristocratic doctrine of government non-interference was replaced, not by any popular reformation, but by increasingly active legislation in favour of the merchant princes. The new throne was made of gold and studded with jewels, but it was set up in the City, not the Palace of Westminster. It was in this world of cut-throat competition and trade rivalry that the puny infant of public health was born. An Act of Parliament designed to check the grossest abuses of filth was passed in the year 1848, but this statute and its immediate successors were so circumscribed as to interfere as little as possible with the trade and profit of those who produced filth. At this time one of the most insistent advocates of public health was the spectre of cholera, and even this gaunt creature had a hard battle against the vested interests of the private water companies. Early in 1854, for example, an outbreak of cholera in Newcastle showed effectively that the disgusting

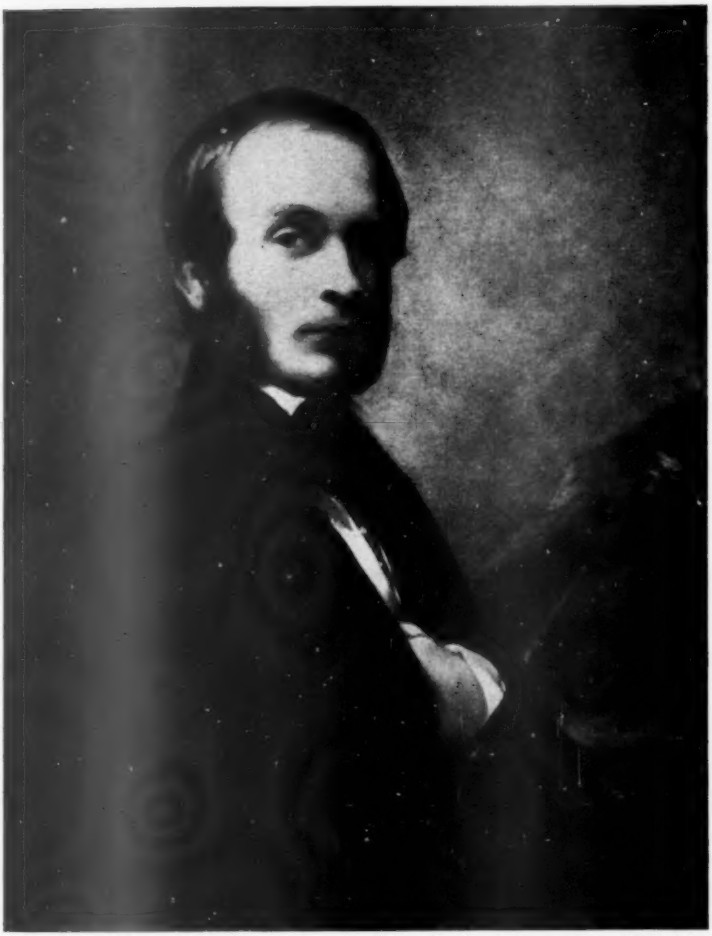


FIG. 1.—John Snow, M.D. 1813–1858. (From the oil painting in the possession of Miss Una Snow.)

conditions of the town were due to nuisances which were a source of profit to some members of the Town Council.

In many parts of London the sanitary conditions were no better. Cecil Woodham Smith, in her history of Florence Nightingale, gives this vivid flash:

"In the summer of 1854 cholera broke out in London, particularly in the miserable undrained slums round St. Giles, to the West of Drury Lane. The hospitals were overcrowded; many nurses died; many, afraid of infection, ran away. In August Miss Nightingale went as a volunteer to the Middlesex Hospital 'to superintend the nursing of cholera patients'. This is the picture: the authorities of the hospital were obliged to send out their usual patients in order to take in the patients brought in every half-hour from the Soho district, Broad Street, &c., chiefly fallen women of the district. . . . The prostitutes came in perpetually—poor creatures staggering off their beat. It took hold of them worse than any, and Miss Nightingale was up day and night, undressing them. The women were filthy and drunken, crazed with terror and panic. . . ."

The local vestry set up a committee to make an enquiry into the outbreak. They began by writing to Sir Benjamin Hall asking for any information about the local outbreak. Hall declined to help, on the pretext that investigations of this kind were more valuable when independent. In spite of this official rebuff the committee got to work. Anticipating the methods of their successors in social science of a century later they started off with a questionnaire. This was unfruitful. Thereupon they embarked upon a house-to-house visitation, with an interviewing team consisting of four doctors (including the experienced Lankester and Snow), two clergymen and a layman. This system worked well, and reports

FIG. 2.—Broad Street, *circa* 1850. (From an original water-colour, London County Council collection.)

of real value were issued. In addition to Snow's report a most interesting corroboration was given by the Rev. H. Whitehead who made a most painstaking personal investigation.

The crucial test of the means of spread of cholera took place in South London, and it was Snow who made the "grand experiment". The issue was made relatively simple by the fact that, shortly before the 1854–55 epidemic the Lambeth Water Co. had begun to supply relatively pure water from the Ditton area, well above the tidal reaches. The Southwark and Vauxhall Water Co., on the other hand, continued to supply (to use Simon's phrase) "the filthiest stuff ever drunk by a civilized community". Snow noted that the areas of the two supplies overlapped, and in places the mains of the two companies went down the same main street. He had no difficulty in picking out the Southwark Company's supply because it contained forty times as much salt as the Lambeth. He found that cholera was fourteen times as fatal in the Southwark supply during an epidemic period. This finding was supported—although with less striking figures—by a committee of enquiry appointed by the General Board of Health.

Why, then, did the issue remain obscure? The first answer was that the housing and the general sanitary conditions of most of the cholera-stricken areas were bad beyond description. No real improvement had taken place since Lord Normanby had informed the House of Lords ten years earlier:

> "I am obliged to remember the negro huts in the West Indies, many hundreds of which I have visited in other days, and I feel bound to admit that before the Emancipation Act, the greatest outcry would have been raised against any proprietor who would have lodged his slaves in such residences as those I have lately seen within a walk of your Lordships' House."

The result of this was that a number of men of goodwill, including Sir John Simon himself, had become so overwhelmed by the Reports on the Sanitary Conditions issued by Chadwick that they were unable to conceive of a specific agent of disease, acting independently of sewage-contaminated water and "fecalized" air.

The second point is that Snow's arguments were attacked by men of ill-will, notably representatives of the waterworks companies:

The most sustained attack upon Farr and Snow was made by an anonymous writer to *The Times* whose letters were subsequently published as a pamphlet. The writer disclaimed any personal interest in the conflict, but he was, in fact, Secretary to the Private Enterprise Association.

The next matter for question is why Snow's views were not more readily accepted by the Medical Press and by his own professional brethren. Snow was an admirable and conscientious medical scientist, and his progress to the Presidency of the London Medical Society shows that his views were regarded with growing respect. Snow was not what might be called a clubbable man; he was a bachelor, vegetarian, teetotaller and a rather solitary worker. Richardson tells us that he had no claims to eloquence nor had he the gift; a peculiar huskiness of voice rendered first hearings from him painful. If he had gone, so to speak, eating and drinking he would probably have gained much more ready acceptance

FIG. 3.—A Court in Southwark. (London County Council collection.)

for his brilliant work, but he tended to be regarded as a crank and indeed the *Lancet* says:

> "Therefore Dr. Snow says gases from animal and vegetable decomposition are innocuous! If this logic does not satisfy reason, it satisfies theory.... The fact is, that the well whence Dr. Snow draws all sanitary truth is the main sewer. His *specus*, or den, is a drain. In riding his hobby very hard, he has fallen down through a gully-hole and has never since been able to get out again."

The personality difficulties of Snow were probably of little account in comparison with the scientific attitude of his age. As early as 1840 Henle had elaborated a germ theory of infection. But his views were not widely accepted. Sigerist has shown that Henle, like Snow, was a man out of his time. The invention of the microscope and the increasing exactness of observation had displaced the age of theory, and people demanded the witness of the eye. An age had passed even before the deaths of Wellington and Melbourne, and a revolution in human thought and action far more dynamic than the Reformation was taking place. The age that was coming to birth was the *Machine Age* of which the so-called industrial revolution was merely a premonitory symptom. This bleak era treated men, women and children as part of their machines. Its masters were far more harsh than the economic theorists of laissez-faire; they were fanatically machine-minded, and their cruelty was as deliberate as it was senseless. In this dark period of British history it is surprising that any advance at all was made towards the removal of causes of disease or the improvement of health.

Snow—An Appreciation

By A. Bradford Hill, C.B.E., F.R.S.

Introduction.—It has been said that "The progress of Science renders useless the very books which have been the greatest aids to that progress. As those works are no longer useful, modern Youth is naturally inclined to believe they never had any value; it despises them and ridicules them if they happen to contain any superannuated material whatever". That will surely never be the fate of a classic that must always fascinate and inspire the student of epidemiology and preventive medicine—John Snow's short treatise "On the Mode of Communication of Cholera". It should be read once, wrote Wade Hampton Frost, "as a story of exploration"—in that sense, I would add, it should be read quickly, for its fascination,—"many times as a lesson in epidemiology". In that sense, like all closely-reasoned statistical studies, it must be taken slowly, carefully and critically with every piece of evidence weighed by the reader and its relevance studied.

What we now celebrate is the centenary of publication of the *second* edition of Snow's masterpiece. The first edition was published in 1849 and it may seem odd that we have, for this celebration, awaited the second. The answer is not so much that the first issue was slender both in size and content, to be swallowed up later in the much enlarged work of 1855, but that this early work could not, in fact, contain the main, and most convincing, part of the observations bearing on Snow's belief that cholera was water-borne. It could not contain that evidence for the very good reason that that evidence did not exist. Snow could not put his views, well developed as they were in 1849, to the critical test until the epidemic of 1854–55. His views were formed in the earlier year and were, as events proved, sound. But they lacked proof. It was the events in London in 1854 and 1855 that could provide the proof and to which Snow unsparingly devoted himself—letting, as Richardson says, nothing personal stand in the way of his scientific pursuits. The results were incorporated in the book of less than 150 pages and published in 1855, a work in the preparation and publication of which, it was said, Snow "spent more than £200 in hard cash, and realized in return scarcely so many shillings".

The Theory

Omitting the illustrative cases, which were many, and the discussion which was full and lucid, the logical development of Snow's theory can be set out in half a dozen sentences taken (or adapted) from his early pages. Thus:

> Innumerable examples show that cholera can be communicated from the sick to the healthy.
>
> Diseases which are communicated from person to person are caused by some material which has the property of increasing and multiplying in the systems of the persons it attacks.
>
> This material, or morbid matter, may be transmitted to a distance, e.g. on soiled linen; in other words proximity to the patient and to his "emanations" is not essential.
>
> Cholera invariably commences with an affection of the alimentary canal.
>
> It follows that the morbid material producing cholera must be introduced into the alimentary canal and not through some other system, e.g. the lungs.

Thus runs the basic theory. And thus, from a consideration of the *pathology* of the disease, Snow first approaches its mode of communication.

The Facts

In support of this theory Snow believes that the instances in which minute quantities of the ejections and dejections of cholera patients must be swallowed are sufficiently numerous to account for the spread of the disease. He seeks to see whether the known facts of cholera fit in with the theory:

> The disease is found to spread most where the facilities for this mode of communication are greatest—amongst the poor, eating, living and sleeping in cramped and crowded quarters. In the better kind of houses it hardly ever spreads from one member of the family to another.
>
> Want of light in some of the dwellings of the poor has often been commented on as increasing the prevalence of cholera. Deficiency of light is a great obstacle to cleanliness; it prevents dirt from being seen and it must aid very much the contamination of the food with cholera evacuations.
>
> On the other hand the *post-mortem* inspection of the bodies of cholera patients has hardly ever been followed by the disease, this being a duty that is necessarily followed by careful washing of the hands; and it is not the habit of medical men to be taking food on such an occasion.

These, and other facts that he advances are not incompatible with the theory but they are clearly insufficient to explain the characteristics of widespread epidemic cholera. And so Snow moves on. "If the cholera had no other means of communication . . . it would be constrained to confine itself chiefly to the crowded dwellings of the poor, and would be continually liable to die out accidentally in a place, for want of the opportunity to reach fresh victims; but there is often a way open for it to extend itself more widely, and to

reach the well-to-do classes of the community; I allude to the mixture of the cholera evacuations with the water used for drinking."

The Water Supply

He illustrates his case against water by accounts of epidemics in London and the provinces, in the army in India and in the Black Sea fleet. I shall pass this evidence by, extremely convincing as some of it is, with but one (unconvincing) quotation. The drainage from cesspools had found its way into the well attached to some houses in a village near Bath and the cholera "became very fatal. The people complained of the water to the gentleman belonging to the property, who lived at Weston, in Bath, and he sent a surveyor, who reported that nothing was the matter. The tenants still complaining, the owner went himself, and on looking at the water and smelling it, he said that he could perceive nothing the matter with it. He was asked if he would taste it, and he drank a glass of it". That, I regret to say, was the end of the poor owner; he was dead of cholera three days later. While, of course, that may be an admirable cautionary tale for "gentlemen belonging to properties" it clearly adds no real evidence to Snow's thesis. The same sequence of events *could* have occurred if the epidemic had been one of plague with its very different mode of spread.

The Broad Street Pump

It is clearly impossible to celebrate the publication of Snow on Cholera without some reference to his most famous field study—that of the Broad Street Pump. Indeed I think it is necessary in this centenary year once more to point out that Snow's claim to fame does *not* rest upon the removal of a pump handle and a *post hoc propter hoc* argument which he would, I believe, have despised. Yet that belief is still widespread. It may well have its origin in Sir Benjamin Ward Richardson's fine memoir of Snow for this is what Richardson wrote:

> "On the evening of Thursday, September 7th, the vestrymen of St. James's were sitting in solemn consultation on the causes of the visitation. They might well be solemn, for such a panic possibly never existed in London since the days of the great plague. People fled from their homes as from instant death, leaving behind them, in their haste, all which before they valued most. While, then, the vestrymen were in solemn deliberation, they were called to consider a new suggestion. A stranger had asked, in modest speech, for a brief hearing. Dr. Snow, the stranger in question, was admitted and in few words explained his view of the 'head and front of the offending'. He had fixed his attention on the Broad Street pump as the source and centre of the calamity. He advised the removal of the pump-handle as the grand prescription. The vestry was incredulous, but had the good sense to carry out the advice. The pump-handle was removed, and the plague was stayed."

It is difficult to resist the final dramatic touch; it is almost sacrilege to attempt to de-bunk it. Yet perhaps it is fair in a centenary year to see what Snow himself wrote. He shows the sequence of events as determined by his inquiry into the 616 fatal attacks which I give below in slightly shortened form.

Date	No. of fatal attacks commencing on each day
August 26	1
27	1
28	1
29	1
30	8
31	56
September 1	143
2	116
3	54
4	46
5	36
6	20
7	28
8*	12
9	11
10	5
11	5
12	1
13	3
14–30	18
Date unknown	45

*Pump handle removed

Though conceivably there might have been a second peak in the curve, and though almost certainly some more deaths would have occurred if the pump handle had remained in situ, it is clear that the end of the epidemic was not dramatically determined by its removal. The deaths had already been declining from a very marked peak for at least five days.

Wholly recognizing these facts Snow himself wrote: "There is no doubt that the mortality was much diminished . . . by the flight of the population, which commenced soon after the outbreak; but the attacks had so far diminished before the use of the water was stopped, that it is impossible to decide whether the well still contained the cholera poison in an active state, or whether, from some cause, the water had become free from it." He never occupied the flimsy pedestal upon which some would place him.

His evidence lay principally in the geographical distribution of the deaths around the pump and in the fact, from his personal inquiries, that almost all the dead had used the pump water.[1] Taken alone, obviously more than one explanation could fit these facts but there were other, and very odd, observations which had to be fitted in at the same time. How was it that the inmates of the workhouse went almost unscathed though surrounded by houses in which deaths from cholera took place? The workhouse had its own water

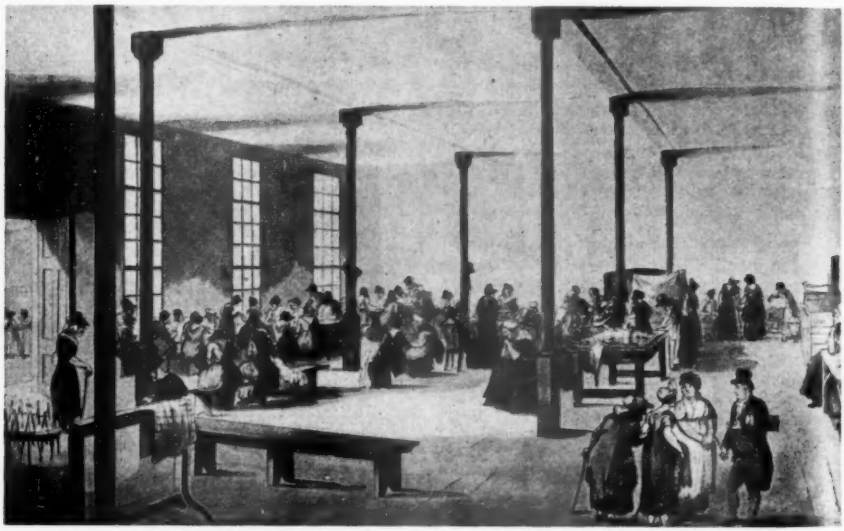


FIG. 4.—St. James's Workhouse, Poland Street. (London County Council collection.)

supply. That no cholera affected the 70 men employed in the local brewery hardly calls for even a rhetorical question and answer. On the other hand at the percussion cap factory where the only vintage supplied was two tubs of Broad Street pump water, 18 of 200 workpeople died. And then there was the astonishing case of the unfortunate widow at Hampstead whose custom it was to have a large bottle of the water brought to her daily and who, with her niece, perished of cholera in a cholera-free area. Snow was right, in my opinion, in regarding that event as "perhaps the most conclusive of all in proving the connexion between the Broad Street pump and the outbreak". But his whole "build-up" of evidence is impressive and should be read in full.

While the scale of the Broad Street disaster and Snow's detailed analysis of it naturally command the limelight, he sets out less well-known but, in my opinion, equally convincing stories. Let, for instance, the reader study the events of July 28 to August 13, 1849, in the "genteel suburban dwellings" of Albion Terrace, Wandsworth Road, where 20 persons died in ten houses and in one house 6 out of the 7 inmates perished. What conceivably could be so local in its effects, leaving untouched "the houses opposite to, behind, and in the same line, at each end of those in which the disease prevailed"? The answer was that they were supplied with water on the same plan, and after the storms of July 26 and August 2 it seems to have been a case almost of "water, water everywhere, nor any drop to drink".

[1]In setting out this information Snow acknowledges the kindness of and the help given him by the Registrar-General of 1855. References in epidemiological papers of 1955 would suggest an inheritance of acquired characteristics.

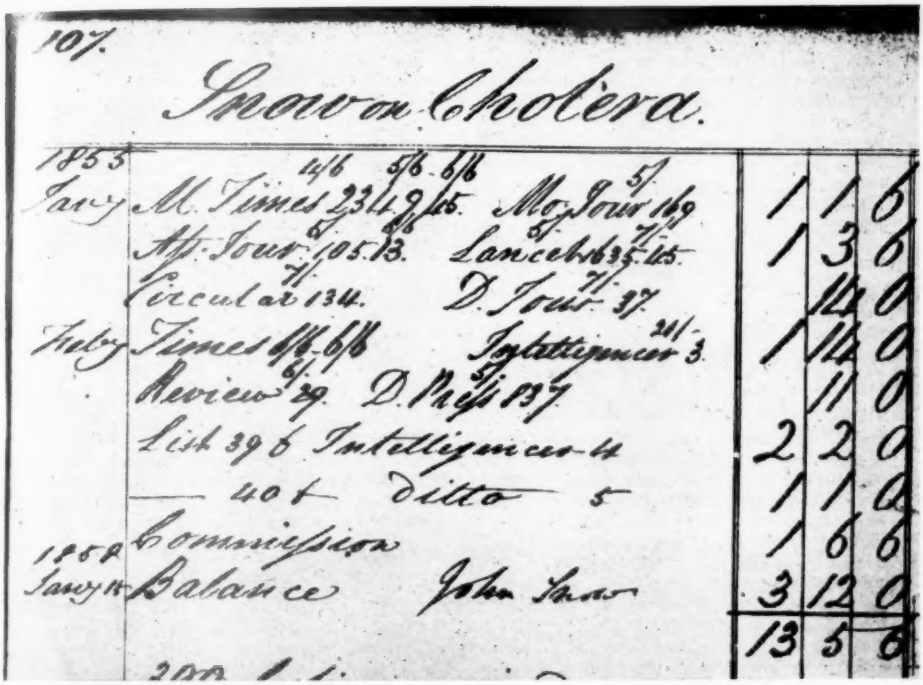


FIG. 5.—An extract from the Publisher's ledgers, showing the cost of advertising, and John Snow's signature in receipt of his profit on sales. 300 copies of the book were printed at a cost of £200 to the author. Only 56 copies were sold.

The following is an extract from "The Times", July 5, 1849. A letter signed by 54 persons.

A SANITARY REMONSTRANCE

We print the following remonstrance just as it has reached us, and trust its publication will assist the unfortunate remonstrants:

THE EDITUR OF THE TIMES PAPER

Sur,

May we beg and beseach your proteckshion and power, We are Sur, as it may be, livin in a Willderniss, so far as the rest of London knows anything of us, or as the rich and great people care about. We live in muck and filthe. We aint got no priviz, no dust bins, no drains, no water-splies, and no drain or suer in the hole place. The Suer Company, in Greek St., Soho Square, all great, rich and powerfool men, take no notice watsomedever of our cumplaints. The Stenche of a Gully-hole is disgustin. We all of us suffur, and numbers are ill, and if the Colera comes Lord help us.

Some gentlemans comed yesterday, and we thought they was comishoners from the Suer Company, but they was complaining of the noosance and stenche our lanes and corts was to them in New Oxforde Street. They was much surprized to see the seller in No. 12, Carrier St., in our lane, where a child was dyin from fever, and would not beleave that Sixty persons sleep in it every night. This here seller you couldent swing a cat in, and the rent is five shilling a week; but theare are greate many sich deare sellars. Sur, we hope you will let us have our cumplaints put into your hinfluenshall paper, and make these landlords of our houses and these comishoners (the freinds we spose of the landlords) make our houses decent for Christions to live in.

Preaye Sir com and see us, for we are livin like piggs, and it aint faire we shoulde be so ill treted.

We are your respeckfull servents in Church Lane, Carrier St., and the other corts.

Teusday, Juley 3, 1849.

Vital Statistics

Another, and, indeed, perhaps the most important, link in the chain of argument lay in Snow's adept handling of the vital statistics of London in relation to its various water supplies. Very briefly, in 1832 the chief villain was the Southwark Water Company with its unfiltered supply from the Thames at London Bridge. In 1849 there is little to choose between the Southwark (now combined with the Vauxhall) and the Lambeth Companies in their capacity, in friendly rivalry, to kill their customers—at a rate of about 1 in 60. And, then, in 1852 the Lambeth Company removed their water-works to Thames Ditton, "thus obtaining a supply of water quite free from the sewage of London". The result is immediately reflected in the contrasting mortality rates of 1853. The rates are relatively high in districts served wholly by the Southwark and Vauxhall Company (114 deaths per 100,000), only half that level in districts served by both companies (60 deaths per 100,000) and nil in the three districts served wholly by the Lambeth Company. There follows, in the epidemic of 1854, Snow's fantastic personal inquiry into every death taking place in the districts served by both companies—"where circumstances were so happily adapted for the inquiry" for "the pipes of each Company go down all the streets, and into nearly all the courts and alleys", "each Company supplies both rich and poor, both large house and small". It is the almost perfect experiment.

Snow was not, however, able to take entire advantage of it. He could compare the absolute numbers of deaths but he did not know the number of houses served by the two water companies in the districts served by both and so could calculate no rates. There was a return of the total houses served by each Company but in using these he must bring into his comparison districts served by one *or* other Company only, thus somewhat vitiating the natural experiment. In a later publication (1856) he has acquired detailed population statistics and is able to reveal that *in every single sub-district* served by both Companies the cholera death-rate of the customers of the Southwark and Vauxhall Company was grossly higher than the rate of the customers of the Lambeth Company; in total the ratio was about 6 to 1. Frost considered that this later paper was "not altogether essential to Snow's argument, which was already well established, but confirms it in detail and shows his keenness in statistical analysis". Personally I think that is an underestimate of its importance. The sub-districts had, in fact, quite widely varying rates; the provision of an exposed-to-risk that allows the contrast of the water supplies *within* the sub-districts is almost fundamental. Snow must have bitterly regretted that he could not do it in his major work. However that may be, the contrast, whether in absolute numbers of deaths or in total districts, was so great as not to be mistaken.

None but the most stubborn, says Frost, could now deny the influence of contaminated water though the way in which it operated was still questioned. As Professor Mackintosh has observed, the stubborn were still quite thick on the ground. It is well to note, too, that the whole of Snow's case rested upon circumstantial evidence, almost entirely upon statistical observations and relationships. Even the not so stubborn were allergic to that kind of evidence—and are still allergic to it.

Conclusion

In conclusion let us, through the eyes of his friend Richardson, look at Snow one hundred years ago, in the epidemic of 1854. "He laboured personally with untiring zeal. No one but those who knew him intimately can conceive how he laboured, at what cost, and at what risk. Wherever cholera was visitant, there he was in the midst. For the time he laid aside as much as possible the emoluments of practice; and when, even by early rising and late taking rest, he found that all that might be learned was not, from the physical labour implied, within the grasp of one man, he paid for qualified labour. The result of his endeavours, in so far as scientific satisfaction is a realization, was truly realized, in the discovery of the statistical fact, that of 286 fatal attacks of cholera, in 1854, occurring in the South districts of the metropolis, where one water company, the Southwark and Vauxhall, supplied water charged with the London fæcal impurities, and another company, the Lambeth, supplied pure water, the proportion of fatal cases to each 10,000 houses was to the Southwark and Vauxhall Company's water 71, to the Lambeth 5."

To those who hold that statistics are dull I commend that simple comparison; to those who hold that the statistical approach is barren and unprofitable I commend Snow on Cholera. "This disease", he concluded, "may be rendered extremely rare, if indeed it may not be altogether banished from civilized countries." How right he was. For close upon 100 years we have been free in this country from epidemic cholera, and it is a freedom which, basically, we owe to the logical thinking, acute observations and simple sums of Dr. John Snow.

Section of Odontology

President—C. BOWDLER HENRY, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

[*March* 28, 1955, continued from November *Proceedings*]

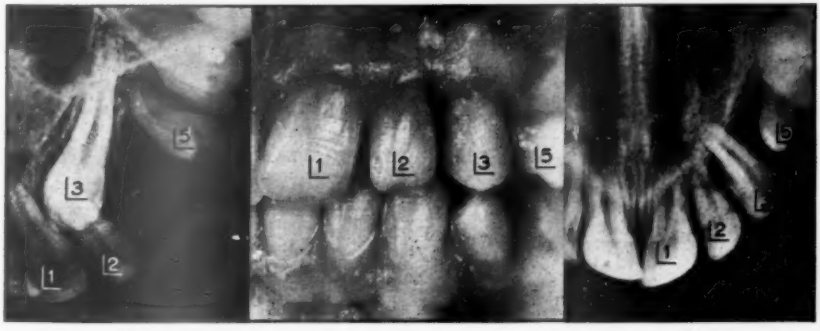
Examples of Reimplantation of Teeth in Young Subjects.—C. BOWDLER HENRY, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

The following cases are examples of the uses of homologous transplantation in the conditions of absence or maleruption of the permanent teeth. I thought it might be possible for teeth, which otherwise would be sacrificed because of being too malplaced to be brought into the line of the arch, to be extracted and replanted in functional occlusion. This is exemplified in Cases I and II. In Case III where a child had had to lose an abscessed upper central incisor I subsequently replanted one of the patient's lower incisors; and in Case IV already reported to the Section (25.1.54, not published) I tried the experiment of transplanting the uncalcified tooth-germ of a lower wisdom tooth into an artificial crypt which I made for it in the mandibular alveolus in place of a congenitally absent bicuspid. So far, these cases appear to be successful.

Case I.—M. C., male, born 1942. Patient shown.
Models showing 54| rotated and in malocclusion (Fig. 1A).
10.5.54: 4| extracted.

A B C

FIG. 1 (*Case I*).—A palatally displaced second premolar transplanted into functional occlusion. A, before operation. B and C, three months after operation.



A B C

FIG. 2 (*Case II*).—A misplaced canine transplanted into normal occlusion. A, before operation. B and C, six months after operation.

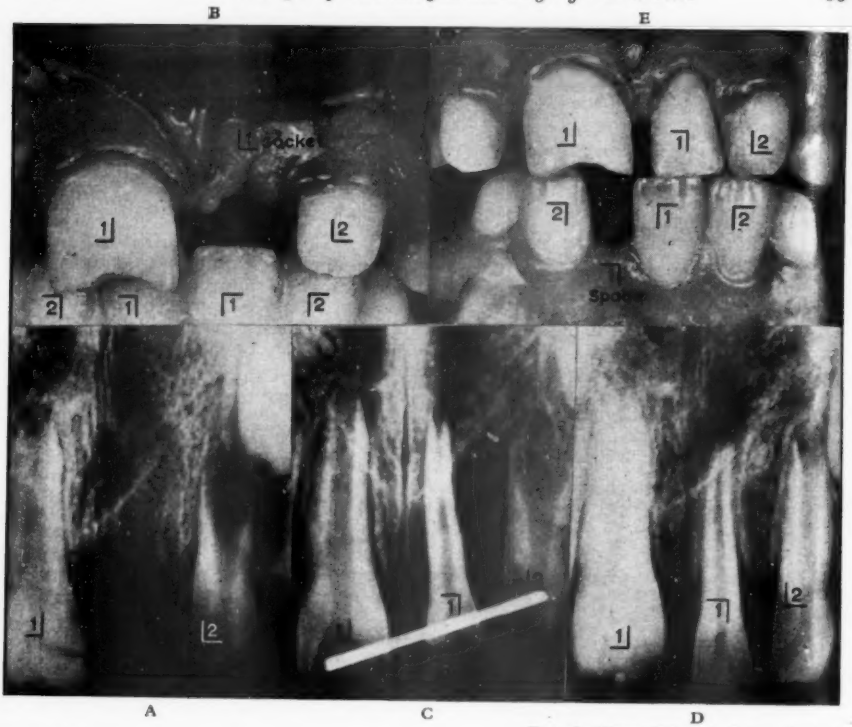


FIG. 3 (*Case III*).—A lower incisor transplanted into the place of a missing upper incisor. A and B, before operation. C, while splinted. D and E, seven months after operation.

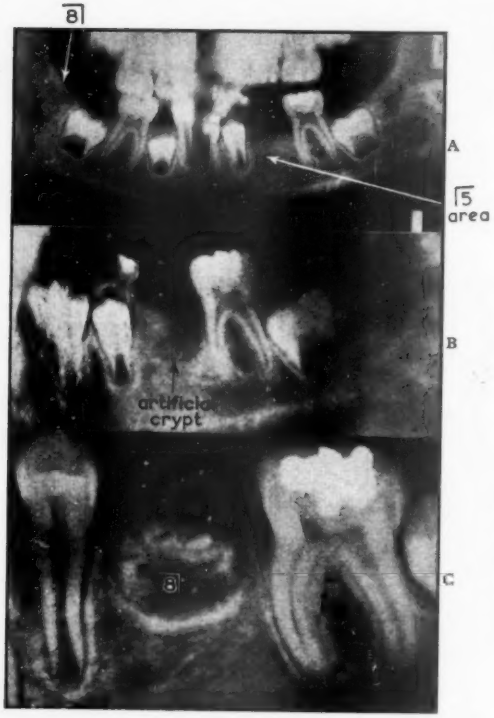


FIG. 4 (*Case IV*).—An uncalcified molar tooth-germ or follicle transplanted into the site of a congenitally absent premolar, showing calcification of crown proceeding. A, before operation, the 8 follicle to be transferred to the site of 5. B, thirteen days after operation, showing artificial crypt in 5 site. C, twenty-two months after operation, showing calcification of molar cusps.

Operation.—13.9.54: Local anæsthesia. $\underline{5}|$ extracted, apex removed and tooth replanted in normal orientation and maintained in an acrylic splint. Splint removed 18.12.54. Photograph and X-ray 21.12.54 (Fig. 1B and C).

Case II.—R. D., male, born 1939. Patient shown. $|\underline{4}$ lost and $|\underline{3}$ absent.

X-rays 6.9.54 showing $|\underline{3}$ unerupted (Fig. 2A).

Operation.—27.9.54: Local anæsthesia. $|\underline{3}$ located in oblique bucco-palatal orientation, removed and replanted in normal position, apex having been amputated. 4.1.55: Splint removed. Photograph and X-ray 19.3.55 (Fig. 2B and C).

Case III.—G. G., male, born 1946. Patient shown.

$|\underline{1}$ trauma, abscess. 9.2.54: X-rays showing $\underline{1}|\underline{1}$, apices not closed. Decision to extract $|\underline{1}$ and later transplant $\overline{1}|$, which, if the graft were to succeed, might be left partially to fill the gap or, possibly, to receive a jacket crown to match $\underline{1}|$. 9.2.54: $|\underline{1}$ extracted. 26.4.54: X-rays and photograph show pre-operative condition (Fig. 3A and B).

Operation: 3.5.54: $|\underline{1}$ socket reopened, $\overline{1}|$ extracted and transplanted into $|\underline{1}$ socket. Fixation by acrylic cap splint with reinforcing wire. Post-operation X-ray (Fig. 3C) 11.5.54. Splint removed 20.7.54. X-ray and photograph 21.12.54 (Fig. 3D and E).

Case IV.—A. H., female, born 1944. Patient not present. Follow-up details of a case originally given as a Casual Communication before this Section (25.1.54; unpublished).

April 1952: X-ray examination disclosed all permanent series present except $|\overline{5}$; $|\overline{E}$ had been extracted (Fig. 4A). Decision to make artificial crypt in $|\overline{5}$ region and transplant complete uncalcified follicle of $\overline{8}|$ into the artificial crypt in $|\overline{5}$ area. Thereafter to enlarge the space between $|\overline{4}$ and $|\overline{6}$ to accommodate the larger size of tooth.

Operation.—10.5.52 as above, the mucosal flaps in $|\overline{5}$ area being approximated by sutures. Healing uneventful. 6.7.53, Schwartz plate inserted for enlarging space ($|\overline{5}$). 23.5.52: Post-operative X-ray (Fig. 4B). 22.3.55: X-ray showing progress of calcification (Fig. 4C).

[*April* 25, 1955]

Congenital Epulis (Granular-cell Myoblastoma or Fibroblastoma) in a Ten-weeks-premature Infant

By GEORGE T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S.Eng., L.R.C.P.Lond.

History.—On 22.2.54 a female infant, H. M., was born ten weeks prematurely after a normal delivery. The mother had infective jaundice. The infant weighed 3 lb. 12 oz. at birth. The only abnormality was a pedunculated tumour growing from the gum of the right lower molar region, making closure of the mouth difficult and suckling almost impossible. Radiographs of the jaws and skull taken one week later showed both bony development and calcification of the unerupted deciduous teeth to be normal.

FIG. 1.—Photograph of the tumour (congenital epulis) taken immediately after removal. The surface of attachment is at the bottom. 1·2 × 0·7 cm.

Operation.—On 2.3.54, at the request of the physician in charge, I removed the tumour under local Xylocaine infiltration. The operation and convalescence were uneventful.

Progress.—When examined a year later, on 8.3.55, the child was a beautiful healthy baby and weighed 16 lb. 7 oz. There was no sign of the tumour, and the teeth and mandible had developed normally, as substantiated by further radiographs.

Macroscopic description of the tumour.—The tumour (Fig. 1) was ovoid in shape, smooth and firm, and covered with normal pink mucosa. Its base, where attached to the gum, was 0·7 cm. in diameter, and its long diameter which projected into the mouth, was 1·2 cm. in length. The cut surface showed a homogeneous greyish appearance.

Histological report.—Section shows an outer layer of keratinized squamous epithelium enclosing very vascular and cellular connective tissue, in which are small numbers of inflammatory cells. The blood vessels are of capillary type, and around them, in the superficial dermis, are numerous spindle-shaped cells with large nuclei and larger rounded cells with abundant granular cytoplasm which does not stain with scharlach R (Fig. 2). In the deeper tissues the lesion is obscured by much cellular vascular tissue (Fig. 3). The appearances are those of "granular myoblastoma".

Discussion.—Probably the first writer to describe such a tumour in a newborn infant was

FIG. 2.—Photomicrograph of superficial area of tumour. × 240. Stained H. and E. This shows the general structure of the tumour. Large round or oval shaped cells with granular cytoplasm form the mass of the field. Here and there are some small vessels. The tumour formation is lying immediately beneath a normal squamous epithelium. Various stains for fat were tried, but were not taken up by the granules.

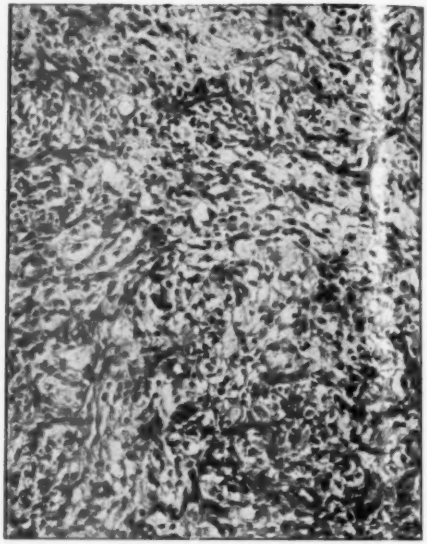


FIG. 3.—Photomicrograph from a deeper vascular portion showing a large number of small vessels and a few round cells, which together rather obscure the granular cells. × 152. Stained H. and E.

Neumann (1871). He called it a "congenital epulis". Abrikossoff (1926) under the title "myoblastenmyome" (reduced by later writers to "myoblastoma") described peculiar growths of the tongue and other parts consisting of large rounded, ovoid or elongated cells with acidophil granular cytoplasm, which in some tumours showed longitudinal and cross-striations and transitions to undoubted muscle fibres, but which in other tumours showed no such evidence of their origin. Horn and Stout (1943) and others applied the name "myoblastoma" to similar tumours of the skin and breast and situations which normally contain no striated muscle, where it was assumed that the tumours "arise from embryonal rests of aberrant myoblastic tissue". Willis (1948) discusses the pathology of this group of tumours at length, and his conclusions are as follows:

"(i) The benign granular-cell 'myoblastomas' of the tongue and of other skeletal muscular tissue are not tumours but degenerative or regenerative lesions of muscle fibre. True neoplasms of this appearance should be called 'rhabdomyomas'.

"(ii) Lesions of similar appearance in tissues where no striated muscle is present should not be called 'myoblastomas'; their muscular nature is unproved."

In fact, Willis considers that the term "myoblastoma" should be discarded altogether. "In spite of the undifferentiated appearance of their cells and not infrequent infiltration of adjacent tissues, these tumours are benign, neither ulcerating, metastasizing nor recurring after removal. Their common sites of occurrence suggest a traumatic origin."

Pearse (1950) in a detailed histochemical and morphological survey of 6 cases of so-called granular cell myoblastoma, advanced the theory that the tumours are "lipoid-containing granular cell fibroblastomas" and regarded the enlargement of the tumour and its infiltrative quality as due to a centrifugal spread of the granular cell change in fibroblasts".

Custer and Fust (1952) added 7 cases of "Congenital Epulis" to some 40 already reported. They varied in size from 5 mm. in diameter to several centimetres and occurred more often in the upper incisor region and mostly in females.

Bauer and Bauer (1953) in a paper entitled "The so-called Congenital Epulis", concluded that the tumour is a "granular-cell fibroblastoma" resembling the so-called "granular-cell myoblastoma", but that it is formed by the transformation of fibroblasts present either in

the sub-epithelial connective tissue, in the peri- and endo-neurium of the nerves of the gum, or in the tooth sac.

Conclusion.—It is evident that the tumour here reported has nothing histologically in common with the traditional "epulis", fibrous or peripheral giant cell, as described by Thoma (1954), but rather that it is a tumour deriving from embryonic cells.

Acknowledgments are made to Dr. C. F. Harris, under whose care the child was warded, Professor G. S. Cunningham and Dr. W. J. Hanbury for the histological report, and to Dr. G. S. Sansom for the photomicrographs—all of St. Bartholomew's Hospital.

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Some Aspects of the Problem of Radionecrosis of the Jaws

By W. DONALD MACLENNAN, L.R.C.P., L.R.C.S., H.D.D., F.D.S. R.C.S.Ed.

AVASCULARITY, necrosis, infection—an ominous triad indeed and yet symbolizing completely the sequence of events in radionecrosis or radio-osteomyelitis (Seldin *et al.*, 1955). The term radio-osteomyelitis infers that all cases of osteoradionecrosis are infected, but this is not so. The degree of involvement of soft tissues will determine whether infection precedes or follows the process of necrosis in the neighbouring bone. While it is true to state that radionecrosis is less frequently encountered at the present time in view of the advances which have been made in radiotherapeutic techniques, the condition, when it does present, still causes considerable concern. The insidious progress, the damage to the local tissues, and the potentially crippling general effect in respect of the patient, do, of themselves, merit attention.

Statistically, the mandibular and maxillary regions, the sole of the foot, and the skin of the lower limb, are most prone to the adverse effects of irradiation. The individual variance in tissue response to therapy is undoubtedly one of the attributable factors (Windeyer *et al.*, 1947).

TABLE I.—EFFECTS OF IRRADIATION OF CELLS IN DECREASING ORDER OF SENSITIVITY

1. Lymphocytes
2. Polymorphs
3. Epithelioid cells
   - (*a*) Salivary gland epithelium
   - (*b*) Basal epithelium (testes and ovary)
   - (*c*) Skin epithelium
   - (*d*) Lung epithelium
   - (*e*) Renal epithelium
4. Endothelium
5. Connective tissue cells
6. Muscle cells
7. Bone cells
8. Nerve cells

Again it would appear that the same tissues in varying anatomical sites will give a different response when irradiated—an observation which was, in fact, made by two of the earlier writers on the subject, namely Recamier in 1905 and Regaud in 1922. The cell response varies with the individual tissue exposure to stress and strain, be it physiological or pathological.

To understand the process of radionecrosis, in so far as it affects the mandibular and maxillary regions, it is necessary to be familiar with the tissues involved, and with the salient anatomical features. The tissues concerned are skin, connective tissues, muscle, bone, dental structures, nerve tissue, vessels, salivary glands, and mucous membrane. It should be appreciated that roentgen therapy, radium therapy and the other forms of radiation employed in the control or treatment of neoplasms do so in essentially the same manner, namely by limitation of cell growth or, in some instances, by actual eradication of the cells concerned. While primarily designed to control cell growth, it is all too obvious that the so-called normal cell may be exposed to considerable danger. The type of irradiation employed, the dosage, and the method of administration are directly related to the effects produced on the tissues exposed. It must be understood, however, that factors of an unforeseen or unassessable nature may predispose to the formation of radionecrotic processes—overdosage with associated massive cell death; "scatter", that is leakage of radiations in the surrounding tissues; the adverse effects of secondary irradiations from bone

(Gratzek *et al.*, 1945); and the superimposition of trauma and/or infection are examples of such deleterious factors.

Histologically, these changes are basically little different from the accepted cell changes in degeneration (Boyd, 1947); and so there are depicted variations from simply cloudy swelling to frank necrosis. Certain features are, however, pathognomonic of radionecrosis. Not least of these are the endarteritis and periarteritis, which are constant findings in all established cases. The vessels show fibrotic thickening of all coats, disruption of the elastic fibres to a greater or lesser degree and, with this, the inevitable predisposition to thrombus formation. Together these factors produce permanent avascularity in an area in which, by virtue of circumstances, there is little chance of an adequate collateral blood supply being established. When bone is involved, the lacunæ and canaliculi are found to be widened and there is, in addition, a considerable loss of the lamellar structure (Ewing, 1926*a*, *b*). It is possible to recognize three basic types of degeneration in so far as they are manifested in bone. These are found singly or concurrently:

(*a*) Proliferative osteoblastic reaction.
(*b*) Rarefactive osteoclastic reaction.
(*c*) Irregular osteitic reaction.

Each presents a radiographic picture, which, correlated with the history, is diagnostic of the condition of osteoradionecrosis. The proliferative osteoblastic reaction is found in these cases which are uncomplicated by infection—a process which is, in fact, similar to the effect of deep X-ray therapy in the treatment of such oral conditions as adamantinoma. With the ingress of infection, rarefaction of bone is apparent and the formation of sequestra is a frequent sequel, as also are pathological fractures. Lawrence (1946) draws attention to the fact that while necrosis is slow in radionecrosis, the formation of sequestra is even slower, hence the irregular osteitic reaction which sometimes presents. In the radiograph there may only be a loss of definition of the cortical bony outline, to indicate the early involvement of bone. Gratzek *et al.* (1945) describe the post-irradiation changes in bone as "frank aseptic necrosis". Unfortunately any necrotic tissue is more prone to trauma and infection. The local resistance of the tissues and the powers of recovery are considerably diminished and so extensive suppuration is a not uncommon complication.

In the treatment of a malignant lesion, this sequence of changes would appear to have an added significance in that if tumour cells, in the course of irradiation, are not destroyed but merely walled off by a limiting barrier of fibrous tissue, these same cells can lead to a recurrence of the original lesion at a later date, should the barrier be exposed to and broken in part or in whole by the ingress of infection. In the presence of infection, full tumour doses of roentgen and radium therapy are contraindicated, and surgery in the presence of radionecrotic tissues is far from satisfactory. It can readily be appreciated, therefore, why it is so vitally important to consider the relative merits of therapy and surgery before embarking on the treatment of the lesion. It is only necessary to witness the failures in both fields to realize that there can be no room for complacency, as long as the patient, following treatment, is exposed to complications which, of themselves, can be so crippling.

So far no mention has been made of the process of repair following exposure of tissues to irradiation. The reason for this is simply that true regeneration is conspicuous by its absence. One explanation, in so far as bone is concerned, surely lies in the fact that, when bone is exposed to the effects of irradiation, the periosteum is easily damaged and may show irreversible degenerative changes quite early in treatment (Watson and Scarborough, 1938). Kanthak (1941) and others have observed that while there may be damage to bone cells, it does not necessarily follow that there are necrotic changes in the surrounding soft tissues. The varying sensitivity of the individual tissues is stated to be in part responsible for this. While it is true that there is a marked variance in the response of the individual tissues to the effects of irradiation, it is felt that in no case showing established osteoradionecrosis are the surrounding soft tissues devoid of the adverse effects of therapy. This fact has been amply borne out in the cases which have come under observation. Again it has been established that in osteoradionecrosis of the jawbones, 83% involve the mandible. It is felt that there are two main reasons for this, namely the marked difference in anatomical relationships in respect of development, blood supply and musculature; and the greater incidence of neoplastic conditions arising in the tissues related to the mandible, the treatment of which by radiation therapy exposes the bone directly or indirectly to the effects of the rays.

The teeth have always been acknowledged to have an important part to play in this problem of osteoradionecrosis of the jawbones. The eternal question is—"Should teeth be extracted before, during, or after therapy?" There are still those who advocate the removal of teeth during the course of, or on the completion of, irradiation therapy (Paterson and Thompson, 1948; Sarnat and Schour, 1950; Cutler, 1951), while others are equally adamant that affected teeth should be extracted before the commencement of treatment (Trotter, 1931;

Slade, 1949). There would appear to be little doubt that teeth, healthy or otherwise, should be extracted and the sockets healed prior to the exposure of the immediate local or surrounding tissues to the effects of radiation therapy. Where the teeth have been retained it is quite common to find that the patient is complaining of acute pain some six to eight months after the completion of treatment (del Regato, 1939). Cervical caries is a not infrequent accompaniment and may eventually lead to fracture of the teeth concerned at the amelo-cemental junction. Stafne and Bowing (1947) discuss the effects of irradiation on teeth and their supporting structures and state that arrested development and necrosis depend on:

(*a*) Intensity of irradiation.
(*b*) Age of the patient at the time of exposure.
(*c*) Length of interval between time of exposure and time of observation.
(*d*) Susceptibility of the patient to the irradiation.

This inevitably leads to a consideration of the effects of irradiation on developing bony structures and teeth. In animal experimentation it has been proven that the more the total irradiation dosage is subdivided, and the longer the interval between the periods of exposure, the less is the inhibiting effect of the irradiations on the tissues concerned (Brooks and Hillstrom, 1933). There is no doubt that if the bones of the face are exposed to the effects of roentgen or radium therapy while they are still in the developing phase, a varying degree of limitation of the growth potential will ensue, which in later life may produce malformation, even asymmetry. The damage to teeth will be dependent, to a large extent, on the stage of development at the time of exposure, and so tooth germs may be destroyed, while at the other extreme there may only be stunted formation of the roots, or delayed eruption of the teeth concerned. The impaired formation of dentine in the developing tooth, the degeneration of the pulp, the damage to the periodontal membrane and fibres, and the gingivitis, which is a common complication in the post-irradiation period, have all been noted (Rushton, 1947; Leist, 1926; Wilson, 1953; Cook, 1952; Smith, 1931). While some of these effects are directly related to the irradiations themselves, others again are indirect. The sequence of caries, gingivitis, necrosis, for example, cannot be explained entirely by the effects of the degenerative processes, although they undoubtedly have a major contribution to make. All cases do not show the progressive caries of teeth, even in the presence of quite extensive osteoradionecrosis, and it would appear to be necessary for the salivary glands to have been exposed to the radiation therapy, before some of the dental pathology presents.

The saliva of the patient showing radionecrosis of the tissues of the oral cavity, is decidedly acid in reaction, is extremely viscous, and may be considerably reduced in quantity when measured empirically over a period of twenty-four hours. Xerostomia is recognized as a complication of irradiation in the treatment of oral malignant disease by Faber (1943) and Furstenberg and Crosby (1945). It is felt that the character of the saliva, in conjunction with the altered bacterial flora of the mouth, is directly related to the caries produced. Progressive cervical caries in the child following therapy is seldom seen, whereas, in the adult, it is a not uncommon finding. As radionecrosis itself is an infrequent occurrence in children, it is extremely difficult to draw any definite conclusions with regard to this matter. Further investigations, however, may prove of value.

Some of the ætiological, pathological and histopathological aspects of radionecrosis involving the jaws have been discussed. It is now proposed to consider a few of the clinical signs and symptoms of the condition, and to outline the general principles of treatment. The secondary repair is essentially a plastic surgery problem and is outwith the scope of this paper. Consider therefore the extreme case of radionecrosis of the oral tissues, complicated by osteoradionecrosis and infection. Here the clinical signs and symptoms are many and varied, and while these are modified in the less severe cases, they are essentially the same. The predominating features may conveniently be tabulated as follows:

GENERAL	(*a*) Loss of weight, associated with debility. (*b*) Toxæmic manifestations.	(*c*) Pneumonic manifestations.
LOCAL	(*a*) Pain. (*b*) Œdema. (*c*) Necrosis of soft and/or hard tissues. (*d*) Osteitis.	(*e*) Progressive dental degeneration. (*f*) Trismus. (*g*) Hæmorrhage. (*h*) Recurrence of the malignant lesion.

Diet.—In the past the importance of diet has not been fully appreciated. The extreme case of osteoradionecrosis is usually associated with severe pain and with a varying degree of trismus. Mealtimes are to those unfortunate patients nightmares, and all too often the daily intake is poor and weight is lost. To build up the resistance of the patient to infection and to improve the general physical condition, it is important to maintain an adequate dietary intake. Individual requirements vary, but it is not uncommon for high calorie diets to be extremely well tolerated, even as many as 3,500–4,000 calories daily. Such figures can be attained by means of supplementary feeds in which fat emulsions play an important

part (Sutherland, 1955). It is thus possible to raise the calorie intake considerably, while restricting the total volume to a minimum. Feeding can be entirely oral, by a special polythene Ryle's tube introduced nasally and kept in the stomach for several months at a time if necessary, or by a combination of these two methods. Again it should be appreciated that a chart depicting the calorie intake and the body-weight can be of value. A persistent drop in the body-weight, despite a satisfactory calorie intake may well provide the earliest evidence of recurrence of a malignant lesion or of metastases.

Pain.—This is an almost constant finding in osteoradionecrosis, particularly in the mandibular region, and is, perhaps, the main symptom of which the patient complains. In the early stages, it is common to find that aspirin, phenacetin and codeine have been prescribed, but despite ever-increasing doses, pain persists. When these drugs are prescribed they should be given regularly, pain or no pain, and supplemented when necessary. Planocaine or Scuroform lozenges may be of value if allowed to dissolve in the mouth just before meals, but they have no lasting effect. Nerve blocks with Eucupin-in-oil, and even ganglion block or sectioning may be necessary in the more severe cases. In the fulminating cases, which are fortunately becoming fewer in number, Largactil, 50 mg. six-hourly, or in selected cases a pre-frontal leucotomy may provide the patient with a means of escape from the distressing pain which can be such a feature of the condition.

The fulminating type of case excepted, there is no one factor which can contribute more to the relief of pain than the surgical removal of the necrotic tissues. The important points to bear in mind when surgical interference is embarked upon are, firstly, the necrotic tissues must be completely removed, so that a normal healing response can be expected from the tissues at the time of the secondary repair—seldom can this be accomplished. Secondly, the future repair should not be a consideration at the time of the primary surgery, in case it should influence the thoroughness of the resection. The aim should be to:

(*a*) Create a defect by removing all the radionecrotic tissues.
(*b*) Encourage primary healing as far as possible by closing the wound.
(*c*) Maintain the tissues in as near to the anatomical position as possible until such time as the final reconstruction can be effected.
(*d*) Reduce infection to a minimum.

In the maxillary region it is sometimes desirable to limit post-operative contraction, and this is possible if a mould is inserted at the time of the resection of the radionecrotic tissues; the addition of a split-skin graft will encourage primary healing and aid in controlling contraction. Again, a skin-grafted cavity can be trained to accommodate a self-retaining appliance at a later date. In the mandibular region resection does not present a major problem, except in those cases in which the resection extends beyond the midline. Here, one of the main problems concerns the control of the tongue and tongue muscles post-operatively, in order to ensure that the airway remains patent. This can be effected by the insertion at the time of operation of an artificial support to which the muscles of the floor of the mouth can be stitched. This may take the form of a silver, tantalum or vitallium bar, or of a plastic prosthesis. Inserts of this type can seldom be considered as permanent, but even if they only remain in situ for a period of three weeks they will have fulfilled their function. In the majority of cases it is necessary to utilize a bar which is of minimum bulk as, after the removal of the radionecrotic tissues, it is frequently not at all a simple matter to effect a soft tissue closure, and a bulky prosthesis could not be accommodated. Immediate bone grafts are, in the opinion of the author, contra-indicated in this field.

In any case in which prolonged respiratory embarrassment can be foreseen there should be no hesitation in carrying out a prophylactic tracheotomy. It is always preferable to perform a so-called "cold" tracheotomy, rather than be faced with a tracheotomy as an emergency measure.

The infection which is invariably present in association with radionecrotic lesions can usually be controlled in three ways:

(*a*) Improvement of the general condition of the patient.
(*b*) Establishment of strict oral hygiene.
(*c*) Antibiotic therapy.

The first of these has already been alluded to. Oral hygiene can be improved by attending to the care of the teeth conservatively and instituting a strict routine of mouthwashes and irrigations, utilizing bland solutions such as bicarbonate of soda in distilled water. Such solutions as hydrogen peroxide should only be used in the weakest dilutions, as they tend to disseminate the infective process into the surrounding tissues. The introduction of the antibiotics has helped very considerably in the control of infection, but resistant strains of organisms are becoming more frequent and this should be guarded against by taking regular wound swabs, culturing them and establishing the sensitivity or otherwise of the organisms concerned in respect of a range of antibiotics.

Hæmorrhage has been cited as a complication of radionecrosis. Martin *et al.* (1940) state that the mortality from this source alone is 10% in such cases. Frank necrosis is not always responsible for this complication. A proportion of cases is undoubtedly complicated by the presence of recurrence of neoplasm, and in such circumstances invasion of a vessel, if it is a large one, must surely be considered as a welcome release from pain and suffering. When such a vessel can be controlled, the cautery is the most efficient way to do so.

To summarize what has already been said with regard to the subject of radionecrosis involving the jaws, it is hardly necessary to reiterate what a crippling condition this can be. Daland (1941) states, as have many other writers in the past, that dental sepsis plays a definite role in the development of osteoradionecrosis of the jaw bones. Indeed this is all too true, but the condition, when it does arise, warrants considerably more concern than the co-relationship to the teeth. Here is a condition which has far-reaching general effects, many of which are irreversible. No one would suggest that poor surgery is an answer to good radiotherapy, but, in so far as the oral cavity is concerned, there would appear to be lesions treated by means of irradiation with the adherent risk of radionecrosis, which could be satisfactorily dealt with by means of surgery. Most of the lesions which can be dealt with successfully by the radiotherapist are amenable to surgery. Radiotherapy has a place in the treatment of malignant disease of the mouth, and in certain circumstances it has no equal. Surely there is a challenge to the workers in both fields to improve both methods and techniques.

The recent paper by Wilson (1955) and his colleagues in respect of the treatment of maxillary neoplasms appeals to the author. The approach to the problem is certainly a rational one—radiotherapy is followed by surgery and finally radium implants are utilized. It is argued that irradiation of a tumour produces the most satisfactory results when the blood supply in the area is unimpaired, and in the absence of previous surgery and/or infection, full doses of radiotherapy can be given. Following irradiation, any surgery carried out is less likely to predispose to dissemination of residual tumour cells. With the latter observation in mind, the biopsy is withheld until 1,000 r has been delivered to the area. Surely such a team approach to the work on neoplasms must offer more than the individual one. If progress is to be maintained, the radiotherapist and the surgeon must co-operate, pool their resources and periodically compare figures on results attained. In this way, the incidence of radionecrotic lesions will be still further reduced.

Irrespective of the methods employed, two- to five-year cures from the ravages of malignant disease may be considered satisfactory from a purely scientific point of view, but there can be little doubt that if one considers the humanitarian aspects, such a life expectancy is far from satisfactory, especially if, as so often happens, even that short span of life is marred by extremes of pain, disfigurement and mental torture.

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Mr. Rainsford Mowlem: The chief feature of excessive radiotherapy or indeed of normal dosages of irradiation, is damage to the vascular supply. This damage is not only immediate, it is persistent and for as long as the patient may live the effects remain. Mr. MacLennan has said that factors of an unforeseen or unassessable nature may predispose towards radionecrosis—namely over-dosage and scatter and also the superimposition of trauma and infection. I do not believe that these factors should be unassessable. Certainly they should never be unforeseen. Any competent radiotherapist can tell whether or not as the result of his treatment there will be bone destruction, and armed with that foreknowledge it should lie within the powers of the surgeon to obviate the dreadful effects of radionecrosis. How he may do so is still a matter of discussion, but much of that discussion is dependent on factors which are not proven but which are still accepted. We must always remember that the damage is mainly to the blood supply so that regeneration is an impossibility. There is, of course, the corollary also mentioned by Mr. MacLennan that this damage inflicted in early life will obviously be followed by failure of development and this may mean permanent disability—permanent disability in the sense that the whole of the tissues in the irradiated area are no longer suitable for surgical intervention. We are faced with the necessity of deciding once and for all that if radiotherapy is to be used then surgery as a subsequent method of treatment is out of the question unless—and only unless—the whole of the irradiated area can be completely removed. No partial excisions, no partial repairs are possible.

Mr. MacLennan goes on to state that in his opinion teeth should be removed prior to irradiation. Is that enough? If it is known that bone is going to be necrotic or likely to be necrotic would it not be preferable to accept this in the beginning? Would it not be preferable to resect the area of bone which is to be destroyed? The timing of such a resection presents some difficulty. We are told by the radiotherapists that operation prior to irradiation might have the effect of spreading the cancerous growth still further. I am not sure how far this is an impression, but it is certainly to my mind a point that needs considerable clarification. I personally am perhaps fortunately situated, in that the Centre at which I work shares a hospital with one of the biggest radiotherapy centres in London. In this combination of two units, the theory is developing that there may be a time shortly after the commencement of irradiation when resection is a perfectly reasonable proposition; when the risk of the spread of the growth is diminished and when there is still a sufficient vascular supply in the area to permit of normal healing.

If such resection is not performed and radionecrosis occurs, there is no likelihood of spontaneous sequestration and regeneration. All that remains is pain and infection and of these pain is the constant and intolerable symptom. MacLennan has stated that in the fulminating cases nerve section, six-hourly sedation or even prefrontal leucotomy may be necessary. He goes on to say of course that "excision of the affected area will cure the pain". There is no doubt that that is true. But I would suggest that we ask ourselves whether as the result of treating one condition, we have any justification whatever for producing pain of a degree that could, under any circumstances, warrant such a procedure as a prefrontal leucotomy. I do not believe we have. In many cases subjected to massive irradiation, there is no likelihood that the disease will be totally cured. All we are looking for is palliation and palliation does not mean the creation of a state of constant pain, of constant purulent discharge, of deformity, and of a total inability to lead a normal life.

MacLennan says that "no one would suggest that poor surgery is an answer to good radiotherapy". Of course it is not. There is no room for poor surgery anywhere; nor for poor radiotherapy. But there is the question as to whether radiotherapy is as good a general answer as surgery. It is obvious that in the fullness of time, and I hope it will not be long, neither surgery nor radiotherapy may have any part to play in the treatment of cancer of any kind. The answer must lie somewhere else. But I would venture to suggest that the damage done by a good surgeon cannot be as irreparable as the damage which may be done even by a good radiotherapist. And it behoves us to choose very carefully when we are deciding on the method of treatment for any condition of malignancy in or near the mouth. Radical surgery will at all events leave behind tissues that are capable of being used as the basis of a reconstruction, a state of affairs which may not exist after radiotherapy. After radiotherapy has apparently controlled the tumour it is to be hoped that there is still a sufficient margin of normal healthy irradiated tissue around it to enable the whole of the treated area to be removed prior to reconstruction. It could be that even more drastic surgery might be the answer. Wherever surgery, good surgery, offers even a reasonable alternative to good radiotherapy, surgery should be chosen. Surgery cannot inflict pain beyond the immediate post-operative phase. It cannot produce continuing avascularity, nor does it produce massive necrosis.

Whenever radiotherapy is used, as indeed it must be used, for those cases in which the diagnosis has been delayed, those unfortunates who have refused to come early enough to be helped, it must be recognized that radiotherapy is being used as a palliative treatment. If that is so, let us use it intelligently. Let the surgeon and the radiotherapist combine together to find the time at which surgery can hope to eliminate the disastrous effects which irradiation must produce if it is pushed to the stage of producing necrosis.

Section of Endocrinology

President—P. M. F. Bishop, D.M., M.R.C.P.

[*April* 27, 1955]

Meeting held at the Postgraduate Medical School of London

Addison's Disease Presenting as Loss of Weight without Pigmentation.—D. Felix-Davies, M.D., M.R.C.P.

The development of methods for assay of melanocyte stimulating hormone (M.S.H.) in human blood and urine by Lerner and his colleagues (Lerner *et al.*, 1954) and its isolation from the human pituitary by Hudson and Bentley (1954) have thrown further light on the mechanism of pigmentation in Addison's disease. Lerner has shown that the excretion of M.S.H. is increased in some cases of Addison's disease, and also that cortisone can decrease an excessive excretion. An increase in pigmentation of the skin and mucosæ is apparent in most patients with untreated Addison's disease and in a recent series of 62 cases, Professor D. M. Dunlop (1953) found it absent in only one. The patient to be reported showed no increase of pigmentation despite severe adrenal insufficiency. During convalescence and whilst on cortisone, he became sunburnt and the skin then darkened normally.

T. R., aged 38. A plasterer. A muscular man of 14 st. 10 lb. until January 1953. A severe rigor followed by anorexia, vomiting and profound exhaustion was diagnosed as tonsillitis. He returned to work three weeks later but was not completely well until six weeks had passed. There were four similar attacks over the next year, and a steady fall in weight of 2 st. occurred during this period. Tonsillectomy was performed in July 1954 and precipitated a further attack of severe asthenia and anorexia from which he did not fully recover although he returned to work. In October 1954 he noticed that heavy exertion caused attacks of sudden extreme weakness and giddiness, which were relieved by lunch or by a cup of sweet tea. Since December 1954 many other symptoms appeared including attacks typical of postural hypotension, paræsthesiæ in the hands and feet, a continued sensation of cold, a reduction in libido and persistent dull epigastric aching.

Past history.—Attack of L. pleurisy with effusion twenty-two years ago. Married with one child aged 18 months.

On examination.—A fair-skinned, fair-haired blue-eyed Irishman, slow in speech, and rather negative in manner (at this time) but obviously worried by his symptoms. No evidence of wasting despite the loss of 4 st. in weight over two years. No pigmentation of mouth, lips or skin folds. A few light brown freckles on upper arms present since childhood. Body hair normal. Intermittently febrile to 99·4° F. with pulse of 80 per minute and B.P. of 80/55 mm.Hg. No other abnormal physical signs.

Investigations.—Urine: Many W.B.C. and white cell casts, but culture sterile. E.S.R. 90 mm. and 83 mm. in one hour (Westergren). Blood picture normal. Chest radiograph showed a large calcified Ghon focus in the left mid-zone, and X-ray of abdomen showed bilateral adrenal calcification. The serum electrolytes were Na 120 mEq./l., K 3·7 mEq./l. (laboratory normal 3·5 mEq./l.), Cl 94 mEq./l. and HCO_3 27·3 mEq./l. Blood urea 42 mg.%. The fasting blood sugar was 87 mg.%, and after 2 units insulin (one-third of standard dose) the half-hourly values were 57 mg.%, 64 mg.%, 64 mg.% and 77 mg.%. E.C.G.: low voltage tracing.

Water load tests (Kepler):

		Control	After cortisone	After ACTH
Night 10 p.m.–7 a.m.		339 ml.	430 ml.	395 ml.
Day	8– 9 a.m.	66	41	68·5
	9–10 a.m.	46	97	40
	10–11 a.m.	48	208	39
	11–12 noon	72	134	84·5
		232	480	272

Cortisone: 50 mg. four hours before test.
ACTH: 50 mg. of ACTH gel I.M. b.d. for two days.
Kepler "A" factor of 7·85.

Hormone assay of twenty-four-hour urine specimens (Dr. C. L. Cope):

	Before	On ACTH	Normal
17-Ketosteroids	3 mg./day	4 mg./day	
Ketogenic steroids	5	3	
Hydrocortisone	Trace	Trace	20–100 μg.
Cortisone	Nil	Nil	20–150 μg.
Tetra-hydro-cortisone	84 μg.	69·6 μg.	900–3000 μg.
Tetra-hydro-hydro-cortisone	29 μg.	12·8 μg.	100–900 μg.

Comment.—There can be no doubt of the diagnosis of primary Addison's disease or of its tuberculous origin. The recent onset of symptoms together with the markedly raised E.S.R. and low-grade fever were taken to indicate activity of the tuberculous process. This was treated by a course of isoniazid and streptomycin which is being contined for nine months.

The adrenal insufficiency was initially treated with cortisone alone, 25 mg. daily, but even when the dietary salt was increased to 16 grams per day, the patient failed to maintain normal weight and electrolyte levels. A depot injection of 50 mg. of desoxycortone trimethyl acetate was therefore added. The patient now feels extremely fit, has normal electrolyte levels and a B.P. of 120/80. He has been provided with scales for daily weighing and is returning to his former occupation involving fairly strenuous manual exertion.

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Addison's Disease with Partial Recovery.—B. E. C. NORDIN, M.D., M.R.C.P.

History.—A. P. joined the Regular Army at the age of 17 but was discharged three years later with a diagnosis of "Fluid round the heart". He remained in good health, however, until the age of 24 when he underwent partial thyroidectomy for non-toxic goitre. About two years after this, he began to suffer from asthenia and malaise, developed pigmentation of the nipples and external genitalia, and was finally admitted to hospital with diarrhœa and vomiting. Oral pigmentation, adrenal gland calcification and hypotension confirmed the diagnosis of Addison's disease. He was treated for about six months with salt and DOCA

FIG. 1.

FIG. 2.

but gradually dispensed with the latter and lost much of his pigmentation. Two years later, on the outbreak of war, he again joined the Army, was passed A2 and remained in the Forces until he was seen by the medical officer who had originally diagnosed Addison's disease and who promptly discharged him. He continued to take salt "as a habit" until the end of 1954, but had since then dispensed with it for three months without ill-effect.

Present illness.—The patient, now aged 43, was admitted as an emergency to Hammersmith Hospital in March 1955 on account of a brief but severe attack of epigastric pain. Routine investigation revealed no cause for this pain but showed numerous calcified foci in both lungs, severe calcification of the pericardium and calcification of both adrenal glands (Figs. 1 and 2). The jugular veins were distended to about 1 cm. above the sternal angle and the patient admitted to some shortness of breath on exertion, but there was nothing else to suggest that he was embarrassed by his pericarditis.

Investigations.—Routine investigation yielded the following results:

Serum sodium	128, 132 m.Eq./l.
,, bicarbonate	29·9 ,,
,, potassium	2·6, 3·8 ,,
,, chloride	98 ,,
Blood urea	23 mg./100 ml.
Hb	109%
Serum proteins	7·5 grams/100 ml.

Glucose tolerance test normal

The following tests of adrenal cortical function were performed:

Water load test—100% excretion in four hours.

17-Ketosteroid excretion—6 mg./twenty-four hours.

ACTH infusion (2 units/hour for six hours.) (Dr. R. I. S. Bayliss): Plasma corticosteroids before infusion 4·2 μg./100 ml.; after infusion 9 μg./100 ml.

Urinary steroids (Dr. C. L. Cope):

	Before ACTH	After ACTH
Compound F	34·4 μg./24 hours	29·6 μg./24 hours
Tetrahydrocortisone	1,594 ,,	1,337 ,,
Tetrahydro F	376 ,,	407 ,,

Sodium depletion test: The patient was put on a diet containing 20 mEq. of sodium and the effect on his urinary sodium excretion, serum sodium and blood pressure is shown in Fig. 3. This test resembles the sodium depletion test of Harrop *et al.* (1933) and the result indicates impaired sodium retention.

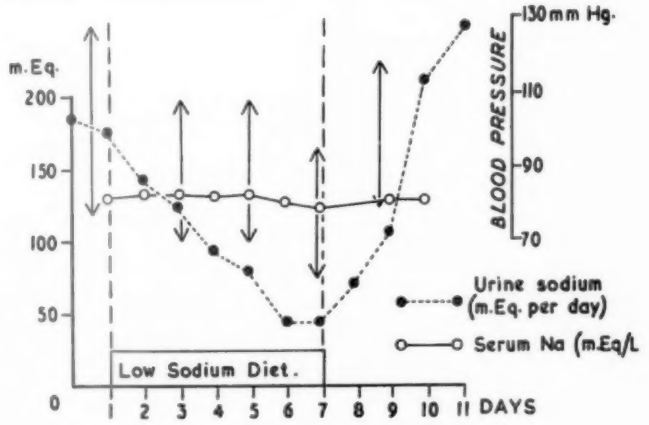

FIG. 3.—Sodium depletion test.

Discussion.—Although the old records of this patient were destroyed during the war, Dr. James Barling, who diagnosed Addison's disease eighteen years ago, confirms that the Addisonian state at that time was unequivocal and that the patient was originally admitted

with vomiting and diarrhœa in what was virtually an Addisonian crisis. The fact that the patient has maintained good health since this without any therapy except added salt, and that he was able to dispense even with this for several months without ill-effect, shows that he is to all intents and purposes no longer suffering from Addison's disease and this is confirmed by his normal water diuresis and serum electrolytes. However, ACTH infusion did not cause the usual rise in plasma corticosteroid levels nor in urinary steroid output. This failure to respond, coupled with impairment of sodium retention, suggests that although the patient has recovered sufficient adrenal cortical function for daily life, his adrenal glands cannot be stimulated to further activity. In other words, he has made a partial recovery.

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Cretinism in Three Siblings.—CRAIG D. BURRELL, M.B., and D. M. T. GAIRDNER, D.M., F.R.C.P.

A family of 4 children was discussed. There was no history of consanguinity in the parents, the family did not come from an area of endemic goitre nor was there any known exposure to a goitrogen.

Three siblings were slow in reaching their milestones, their X-rays revealed gross delay in ossification of epiphyses with marked "stippling" of those epiphyses present, and their plasma cholesterol concentrations were raised (287 mg.% to 350 mg.%). The thyroid gland was normal in two, and very slightly enlarged in the third child. In the 2 children so far treated with thyroid replacement therapy, growth and development have been accelerated and plasma cholesterol concentrations lowered (to 185–225 mg.%). A fourth sibling was normal in all respects.

Radioiodine studies on the three cretinous siblings revealed high and avid uptake by the thyroid gland together with raised plasma protein-bound radioiodine forty-eight hours after the administration of the ^{131}I. Exhibition of Neo-Mercazole and perchlorate produced a slight increase in urinary excretion of radioiodine.

These cretins, unlike those described by Stanbury and Hedge (1950), have a normal iodide-trapping mechanism. It would appear that these cases are similar to those reported by McGirr and Hutchison (1953), and Stanbury *et al.* (1955), in that iodide is incorporated into an organic compound which is released into the circulation, resulting in a high level of plasma protein-bound iodine, but that the compound is not a potent hormone. It seems possible that this compound may be di-iodo-tyrosine. Paper chromatographic studies of the plasma from the three siblings here reported are under way.

It is interesting to note that the cretins here studied have no significant thyroid enlargement, in contrast to similar cases reported by Stanbury and Hedge (1950), Hubble (1953), McGirr and Hutchison (1953), Wilkins *et al.* (1954) and Stanbury *et al.* (1955).

A full report on these cases will be published later.

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Cobalt Goitre.—H. BREIDAHL, M.D., and RUSSELL FRASER, F.R.C.P.

R. R., male, aged 21 years. First seen in October 1954 with the complaints of life-long nocturia, and pallor and shortness of breath for six months. He had no relevant past history, but a brother had died at the age of 16 with "renal rickets".

In November 1954 the following results were obtained from tests.

(1) Blood urea 131–172 mg.% on numerous occasions.

(2) Hb 44%, R.B.C. 2,430,000, M.C.V. 61 cu.μ. Microcytic anæmia. Serum protein: Total 7·6 grams%, A/G ratio 1·9/1.

(3) Urine: Albumin always greater than 1 gram daily. Sugar—green to Benedict's on 5 occasions. Fixed Sp. Gr. 1008–1010. Microscopy—normal. Normal aminoaciduria.

(4) Glucose tolerance test: F.122, ½-hr. 140; 1-hr. 146; 1½-hr. 89; 2-hr. 75 mg.%.

He was given blood transfusions, but as his hæmoglobin failed to stay at satisfactory levels with the usual hæmatinics, he was started on cobaltous chloride 50 mg. t.i.d. late

December 1954. This produced a reticulocytosis of 1·8% and a satisfactory hæmatological response, so he was maintained on that dosage.

He continued well until March 1955 when he noticed a swelling of the front of the neck. This persisted and increased, and became hard and painful. On April 8, 1955, cobalt therapy was stopped and, on April 12, 1955, he was admitted to Hammersmith Hospital for investigation; over these four days the swelling had decreased in size and become softer.

Examination revealed a thin, pale young man of short stature. There was a huge, firm swelling of the thyroid gland, about 100–120 grams in size. There was no bruit over the gland, and no clinical evidence of thyrotoxicosis or of myxœdema (Figs. 1 and 2).

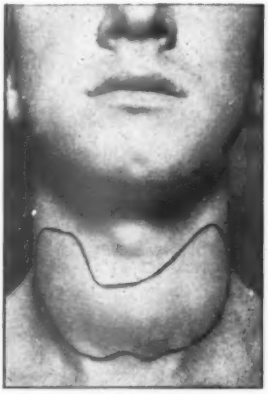

FIG. 1.

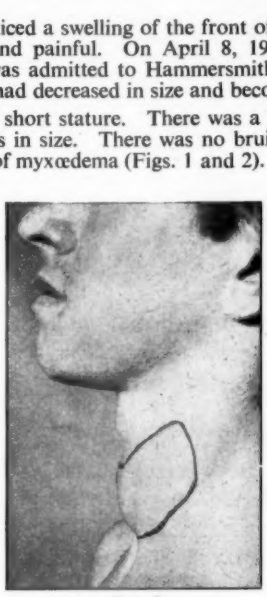

FIG. 2.

Results of tests were as follows: Hæmoglobin 88% (13·1 grams%). W.B.C. 5,000. Blood urea 154 mg.%. Serum cholesterol 334 mg.%, bicarbonate 18·6 m.Eq./l., sodium 126 m.Eq./l., chloride 103 m.Eq./l., calcium 10·6 mg.%, phosphate 6·8 mg.%. Insulin tolerance test was normal.

Urine: Findings the same as previously. B.M.R. —19% unsedated. X-ray bones normal.

^{131}I test showed rapid uptake and conversion to protein-bound ^{131}I. Early thyroid clearance: 22·3% of extracellular fluid per ½-hr. 48-hr. neck uptake: 64·1%. 48-hr. urinary excretion: 7·54%. T: 34·6. 48-hr. P.B.^{131}I=0·9% administered dose per litre (normal 1–10%).

The tests indicate: (1) Definite hæmatological response to cobalt. (2) Chronic renal insufficiency. (3) An active, avid thyroid gland, four days after stopping the cobalt, which had probably been undersecreting (low B.M.R.): suggesting recent antithyroid drug administration.

Comment.—With the use of cobalt in the treatment of the anæmias of chronic nephritis, chronic infections and rheumatoid arthritis, and of sickle-cell anæmia, satisfactory hæmatological responses have been obtained without serious side effects, provided the tablets have an enteric coating to prevent nausea. However, there have been two recent reports (Gairdner *et al.*, 1954; Kriss *et al.*, 1955) of goitre developing during cobalt administration and, until more is known of this action, we feel caution must be exercised in the use of cobalt as therapy for anæmia. The goitrogenic action of cobalt is probably due to its action, as a heavy metal, in inhibiting an enzyme system, as suggested by Kriss *et al.* (1955), and we are investigating this suggestion further.

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Section of the History of Medicine

President—Sir ZACHARY COPE, M.S., M.D., F.R.C.S.

[*April* 6, 1955]

Katherine Mansfield's Illness [*Abridged*]

By BRICE CLARKE, M.D.

KATHERINE MANSFIELD (Mrs. Katherine Middleton Murry, *née* Kathleen Beauchamp) was born in Wellington, New Zealand on October 14, 1888. Her family was of English Colonial stock and had been in New Zealand for several generations. Childhood in Wellington ended in January 1903, when Kathleen and her two elder sisters sailed for England with their parents. The girls spent the next three years as boarders at Queen's College, Harley Street. Kathleen continued to write, starting a journal and contributing to the College magazine. She read modern English and Continental literature avidly, including Oscar Wilde, whose cynical philosophy awakened a response in some part of her complex personality. She also studied music seriously, taking lessons in the 'cello at the neighbouring Royal College of Music. But in 1906 the parents arrived in London to take their daughters back to New Zealand. Kathleen's hopes of a musical career were extinguished and the project of the eighteen-year-old girl to share a flat with a friend in London came to nothing.

The Beauchamp family returned to Wellington in December 1906. After a long struggle, in the course of which she showed unconcealed dislike for life in the Dominion, her father yielded to her wish to live in England and gave her an allowance of £100 a year. This sum was increased later and was supplemented several times by special payments during illness, and by help from K. M.'s life-long friend, Miss Ida Baker.

In the 1950s a young woman coming to London with limited means would probably seek suitable work, or take a systematic course of study or training. But Katherine Mansfield's purpose was the pursuit of *art* and *life* and she may have been temperamentally incapable of submitting to the discipline of a regular occupation. "I do not want to earn a living: I want to live", a quotation from Wilde, was recorded in her reading notes before she left New Zealand. In March 1909 she married Mr. George Bowden, but left him after the wedding night. Shortly after her marriage, it appeared that she was pregnant, and that Mr. Bowden was not the father. Miss R. E. Mantz wrote of her life about this time: "She was eager for essential experience and even eager to pay the price for it. Probably she could have given to herself no account of the hunger which possessed her and drove her on".

In the spring of 1909 K. M. was using veronal to induce sleep but apparently succeeded in breaking the habit soon. Mrs. Beauchamp travelled from New Zealand to see her daughter, who then went to live in the small Bavarian spa, Wörishofen. In the autumn or early winter of 1909 there was a premature confinement and stillbirth, said to have resulted from lifting a trunk to the top of a wardrobe. K. M. had a serious illness in Germany during her pregnancy, having contracted a chill by walking barefoot in the woods. Her experiences in Germany are reflected in the first published volume of stories, "In a German Pension". The loss of the child caused "great mental agony" but K. M. regained strength and returned to England in January 1910.

K. M. was seriously ill in the spring of 1910 and underwent an abdominal operation in a nursing home; in the summer of 1911 she was ill again with pleurisy. In the spring of 1911 she took a flat in Gray's Inn Road, at a rent of £52 a year. She was often hungry and resorted to 1/3d. dinners at the "Dieppe". In 1912, her biographer, Miss Mantz, mentions another attack of pleurisy. About April 1912 K. M. established a permanent relationship with Middleton Murry. Owing to delay in divorce proceedings they were unable to marry until 1918. Middleton Murry shared the twopenny meat-pie dinners to which the young

authors were sometimes reduced. These low calorie meals were supplemented by visits to the saloon bar of the "Duke of York". Middleton Murry has written of their life at this time. "We fed at the cheapest of cheap restaurants, and even persevered, until our stomachs could stand it no longer, at a meat-pie shop, where a pie was a penny, potatoes a halfpenny—twopence in all for dinner." At one time they lived in a room in Chancery Lane at ten shillings a week, furnished with a camp bed, two chairs and a packing case. In the summer of 1913 K. M. was again unwell and later in the year, while living in the cold, damp "Rose Tree Cottage", outside London, she suffered from fibrositis.

In December 1913 the lovers went to Paris. It was very cold, "money dwindled at a terrifying speed", and before they returned, the *femme de ménage* took K. M.'s overcoat. In March 1914 they were back in London, and they were both ill with pleurisy. The doctor who attended them refused to send on a bill. Their economic position was not improved by the outbreak of the 1914 war and they spent a miserable winter "in a damp and draughty cottage in Great Missenden . . . during part of which K. M. was crippled by arthritis".

In October 1915 K. M.'s only brother was killed by a bomb explosion on the Western Front, and the shock of this event affected her greatly. In December she left for Bandol on the Mediterranean, where she remained until April 1916, with considerable benefit to her health.

In the autumn of 1917, K. M. was again seriously ill, and embarked on a second visit to Bandol in January 1918. This proved a dismal failure. War conditions in France had become worse and her return journey in March–April 1918—at the height of the crisis caused by the last German offensive—would have been a severe ordeal even to a healthy person. K. M. left England again in 1919, and until her death in January 1923 travelled in search of health in Italy, Switzerland and France, returning to England in the summers of 1920 and 1922.

Katherine Mansfield died of pulmonary tuberculosis at the Gurdjieff Institute in France, an establishment for spiritual healing. Many people who knew her, including probably some of her doctors, are still alive. The following analysis of her illness is based entirely on the published Letters and Journal, on Middleton Murry's biographical notes and on other material in published biographies.

In May 1910 K. M. had an attack of "rheumatic fever", while convalescent from an abdominal operation. Following this febrile illness, the first recorded attack of pleurisy in July 1911 is highly significant. Early in 1911, K. M. was with child again, but this pregnancy was terminated. In 1913, there were further symptoms of ill-health, attributed to fibrositis. In March 1914 K. M. was ill with pleurisy again and was attended by Dr. Croft Hill. *This was the third recorded pleurisy.*

In the winter 1914–15 she was "crippled by arthritis". In March 1915 she wrote: "it is raining hard and my lung hates the weather." In December 1915 K. M. wrote that she was free from rheumatism for the first time for a year. Middleton Murry has written as follows about the pain in the chest in 1915: "the illness . . . was a rheumatic pain which had a pernicious effect on the action of the heart. It had no connection with the pulmonary tuberculosis of which she died. This did not appear until two years later, in December 1917. K. M. was always convinced that she would die of heart failure." The winter in Bandol (December 1915–April 1916) proved beneficial but letters written in the summer of 1917 show that K. M. did not feel well.

In the autumn of 1917 K. M. was again ill and her weight had fallen from nine and a half stone to eight stone. In December 1917 a medical certificate, obtained for the purpose of a second visit to Bandol, stated: "That left lung of mine that had the loud deafening creak in it is no end better but there is a spot in my right lung, which confirms him in his opinion that it is absolutely imperative that I go out of this country and keep out of it through the future winters" (K. M.'s letter to Middleton Murry). In another letter to Anne Estelle Rice she wrote: "the doctor says I must never stay in England for another winter, but must leave in September and not come back until April." Referring to a journey to Garsington in November 1917, Middleton Murry wrote: "K. M. caught a severe chill, which ultimately developed into tuberculosis." In December she was in bed in her Chelsea flat with a high fever and wrote "I lie in bed in a kind of furious bliss". There was evidently a serious extension of her pulmonary tuberculosis at this time, with marked toxæmia. There was no further deterioration in her health during the second brief stay in Bandol. There was no systematic regime of rest in bed. She wrote in January 1918: "I stay in bed every day . . . if it is fine I go for a small walk in the afternoon." And a few days later. "Why don't I get up now and sit at the table and write before lunch? No, I can't. I am too tired. I have overdone it these last perfect days and walked too far and have been out too long." And in February: "I'll go for a big walk this afternoon." On February 19 hæmoptysis occurred for the first time. When she returned to England in April 1918 Middleton Murry described her as "a gaunt and bright-eyed shadow of what she had been four months before". I

October 1918 she was examined by a London specialist, who advised that the only chance of recovery was treatment in a strict sanatorium. "If not, she has two or three years to live, four at the outside." The reaction of the patient was that a sanatorium would kill her. Most of the rest of her life was spent on the Continent. She went to San Remo in September 1919, moved to Mentone in February 1920, and returned to England, apparently improved in health, in April 1920. She left England again for Mentone in September 1920, and was seriously ill in December. About that time a tuberculous gland in the neck had to be drained. Early in 1921 "Spahlinger's treatment" was considered, but the alternative of residence at Montana in the Swiss Alps was adopted. In 1922 Dr. Manoukhin's treatment by irradiation of the spleen was tried, naturally without benefit. She died, almost literally on her feet, a few minutes after a sudden hæmorrhage on the stairs of the Gurdjieff Institute, on January 9, 1923.

It is clear that K. M. was ill with tuberculosis from 1911. It was well understood at that time that pleurisy was a precursor of phthisis or, as one prefers to express it now, was an early stage of phthisis. Why was the warning of repeated pleurisy unheeded? There are at least three alternative explanations: (i) The diagnosis of phthisis was not considered before 1917. (ii) Phthisis was suspected but the patient was not clearly warned of the position. (iii) Tuberculosis was rejected by the patient as the cause of her illness, until failing strength and unequivocal symptoms forced her to concede the fact of tuberculosis in December 1917. The available evidence is insufficient for a definite answer. There is, however, no record that K. M. was told that she had tuberculosis until 1917.[1]

K. M. was endowed with beauty, good physique and abundant vitality. A photographic group in 1903 shows her as a robust, full-faced girl; with broad shoulders. Photographs dated 1910 and 1911 convey the impression of health, but a photograph taken in 1913 suggests the phthisical facies. A reproduction of a miniature painted in 1914 conveys the same impression. The last published photographs (1921 and 1922) show unmistakable evidence of the chronic poisoning of advanced pulmonary tuberculosis. Mr. Kingsmill described K. M. about 1911 as "sturdy, dark-haired, with a fringe over her forehead, and dark hostile eyes". She was a superb swimmer. In 1913 Frieda Lawrence described her as "exquisite and complete, with her fine brown hair, delicate skin and brown eyes, which were later called her gu-gu eyes". Her life story illustrates many of the predisposing factors of pulmonary tuberculosis. The conflict with her family in New Zealand, the unhappy events of 1909, the abdominal operation in 1910, the second pregnancy in 1911, the comfortless racketing life in the bohemian world of London and Paris with insufficiency of food, heating and possibly even suitable clothing must have lowered resistance to the infection, which probably occurred in 1910. K. M., having contracted tuberculosis, had traits of character which were fatal to the hope of recovery. Complete inability to accept the fact of tuberculosis and to rearrange her life in accordance with medical advice was the essential cause of her death. The shock of the loss of her only brother was extremely severe and may have contributed to neglect of health, by accentuating an unconscious death wish. While a part of her rebelled against external restraint or domination, another part embraced "the flight into illness". She wrote to Anne Estelle Rice about December 1917: "When I heard the medicine man say: 'You ought to go to some place like Teneriffe or Madeira, but as you can't go there, Spain or the South of France will do,' I would not have swopped my lung with any man alive. If I stay in England he says I may become consumptive. Alors, je m'en vais." Inability to follow medical guidance may have arisen from the same impulses which caused her to revolt from parental control in childhood and adolescence. Hartz (1954) considers that acceptance of the passive role is the outstanding problem of the majority of tuberculous patients whose emotional reactions cause difficulties. He adds that the personal problems of passivity are found chiefly in patients with a history of disturbed relationships in childhood, usually mainly with the mother. In 1918, K. M. wrote to Middleton Murry. "I have discovered the *only treatment* for consumption. It is *not* to cut the malade off from life: neither in a sanatorium nor in a land with mild rivers, butter mountains and cream valleys. One is just as bad as the other. Johnny Keats' anchovy has more nourishment than both put together. Don't you agree?" Wittkower (1949) has shown that the course of phthisis is much less favourable in those patients who erect psychological defences. The duration of the illness from 1911 to 1923 is a proof of her high vitality and constitutional resistance.

One may accept that K. M. was ill with tuberculosis from 1911 until her death in 1923 but there is no evidence of any enhancement of her gifts by the toxæmia of the disease before 1917. The biographical evidence shows that chronic tuberculosis drained her vitality, promoted personality changes, limited her opportunities for normal experience and tended to cut her off from a big part of life. But all her best work was written after the serious

[1] Mr. J. Middleton Murry, in a personal communication, has stated that Dr. Croft Hill did not mention tuberculosis at the time of the pleurisy in March 1914.

breakdown in health in 1917.[1] This suggests that toxæmia and the knowledge of impending death heightened her perceptions and enabled her to achieve the artistic perfection for which she had striven all her life. The stories, the Journal and the Letters remain to show the unique quality of her gifts and to suggest the extent of the world's loss from her early death.

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[*May* 4, 1955]

Dr. Addison and his Work

By P. M. F. BISHOP, D.M., M.R.C.P.

THE 1855 MONOGRAPH

IN May 1855 Thomas Addison [1], then Senior Physician to Guy's Hospital, published a slender monograph, richly illustrated with coloured lithographic plates, entitled "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules", and thereby attributed, for the first time in medical history, a general morbid condition to a defect of a ductless gland, an achievement which, as Sir Henry Dale [2] suggested in his Addison Lecture of 1949, entitles him to be regarded as the founder of Endocrinology. The treatise is couched in elegant language and the clinical picture is portrayed vividly and with remarkable accuracy, even by modern standards.

Addison described the classical features of what to-day is known as adrenocortical deficiency or Addison's disease—the slow onset, the asthenia, the gastro-intestinal symptoms, the hypotension, the loss of weight, the pigmentation and even the occasional association of vitiligo. Furthermore he drew attention to the fact that the adrenal glands were diseased. It is true that he also mentions anæmia and, though there is usually a mild secondary anæmia, it is not a prominent feature. Though he was in no hurry to publish his findings—he was 62 when this, his last and most famous publication, appeared—he might well have been forestalled in his discovery, for the condition was undoubtedly not a new disease.

PREVIOUS KNOWLEDGE CONCERNING THE SUPRA-RENAL CAPSULES

The adrenals were first depicted in one of the beautiful series of copper-plates on human anatomy made by Eustachius in 1552. Unfortunately these were immured in the Vatican Library until Pope Clement XI consented to their publication by his physician, Lancisi [3], in 1714. Jean Riolan [4] named the glands the "supra-renal capsules" in 1629, though they had previously been called the "atrabiliary capsules" by Caspar Bartholinus [5] the Elder of Copenhagen because they were supposed to contain black bile. In the early part of the eighteenth century a prize was offered by the Académie des Sciences of Bordeaux for an essay on "Quel est l'usage des glandes surrénales?" As no one was able to put forward any plausible answer the prize was not awarded, and it must have seemed that they received the coup-de-grace at the hands of François Magendie [6] in 1841 when he remarked that as no one any longer believed in black bile, the adrenals "had ceased to be secreting agents". It was in this atmosphere of scepticism that Addison began by careful observation and diligent post-mortem studies to unveil the consequences of deficiency of these small glands.

[1]The first version of "Prelude" was written in Bandol in the winter 1915–1916.

Reactions to the Monograph

The Monograph was received in this country with mixed feelings. Some, such as Hughes Bennett [7] and other professors at Edinburgh, where Addison had obtained his M.D., denied the existence of the disease and papers were written in Germany and France with the same object. The reports of two or three cases presented before the Royal Medical and Chirurgical Society—now, of course, the Royal Society of Medicine—were not accepted for publication in the Society's *Transactions*. This distressed Addison greatly for in 1849 and 1850 he had actually held the office of President of the Society. Nevertheless, Addison had some staunch and loyal supporters, such as Jonathan Hutchinson [8] and Trousseau [9] who gave the condition its eponymous title "La maladie d'Addison" in 1856; and, of course, his faithful pupil, Samuel Wilks, who had goaded Addison on to write the Monograph and had done all the dissections and possibly much of the writing for it, for Addison was a reluctant author and the total output of his scientific papers numbered no more than 14, and 3 of these were written jointly, one with Bright, one with Gull, and the third with Morgan. (This does not include the textbook of medicine, which he wrote with Bright [10]. Only the first volume of this appeared and it is believed that Addison wrote most of it. It contains the earliest accurate account of appendicitis.) By far the most important immediate consequence of Addison's Monograph was that it stimulated the ebullient Charles Edouard Brown-Séquard [11] to remove the adrenal glands from an assortment of experimental animals and to deduce from the fact that all succumbed that they had died of Addison's disease and that the adrenal glands, therefore, contained a principle which was essential to life.

Further Development of Knowledge Concerning the Adrenal Glands

But after 1856 the adrenal glands descended into a scientific limbo and it was forty years before Oliver and Schäfer [12] demonstrated the presence of a pressor substance in the adrenal medulla. In 1901 Takamine [13] and Aldrich [14], independently, isolated adrenaline in crystalline form, and in 1904 it was synthesized by Stolz [15]. In 1914 Cannon [16] propounded his "emergency" theory of adrenal medullary function. In 1926 Rogoff and Stewart [17] embarked upon studies which revealed that adrenocortical extracts possess life-saving properties, and thereby vindicated the conclusions reached by Brown-Séquard. In 1928 Szent-Györgi [18], searching for a powerful reducing agent in the adrenal cortex, discovered vitamin C. In 1930 Swingle and Pfiffner [19] produced a life-preserving principle from the adrenal cortex which was employed as the first rational therapeutic agent in Addison's disease. In 1934 Kendall [20] isolated corticosterone in crystalline form and in 1937 Reichstein [21] prepared deoxycorticosterone acetate synthetically and this was first used in 1938 by Leonard Simpson [22] in the treatment of Addison's disease. In 1949 Hench launched cortisone upon an hysterically excited medical world [23]. In 1952 Tait, Simpson and Grundy [24], at the Middlesex Hospital, extracted a potent salt-retaining compound from the adrenal cortex which was subsequently isolated in pure crystalline form and its chemical structure determined by Reichstein and the Middlesex group [25], and is now known as aldosterone. Even more recently halogen derivatives of cortisone have been found to possess immensely great potency [26]. Prednisone and prednisolone are the latest additions to the group of therapeutic cortisone derivatives.

Addison as a Dermatologist

In the Monograph Addison laid great emphasis on the pigmentation, and undoubtedly this feature originally drew his attention to the disease. For Addison was one of the most distinguished dermatologists in the country and the first "Lecturer on Cutaneous Diseases" at Guy's, thus establishing the Skin Department there. It was only because he was so anxious to avoid being considered a specialist that he delayed publishing his descriptions of vitiligoidea (or xanthelasma), jointly with William Gull, until 1851 [27], and of morphœa until 1854 [28]. One of the patients reported on by Addison and Gull suffered from diabetes and they therefore gave the first account of xanthoma diabeticorum.

There exists to the present day in the Guy's Hospital museum a remarkably fine—indeed I think unique—collection of wax models depicting diseases of the skin and made by Joseph Towne, who was introduced to the Hospital in 1826 when a mere lad of 18, by Sir Astley Cooper, and served it for fifty years. It was under Addison's direction that Towne built up this collection of wax models of the skin diseases.

Addison's Anæmia

It is probable that Addison's interest in dermatology was responsible for drawing his attention to the peculiar discoloration of the skin in pernicious anæmia, for in 1849, six years before the publication of the Monograph, he communicated a paper to the South London Medical Society entitled "Anæmia—Disease of the Supra-renal Capsules" [29].

As in the case of Addison's disease, he paints a vivid and accurate clinical pictur of pernicious anæmia, a remarkable form of anæmia, which, although incidentally not ed by various writers, had not attracted, as he thought, by any means the attention it r lly deserved. It was a state of general anæmia in adult males, and had for several years ast been with him a subject of earnest inquiry and of deep interest.

Who Discovered Addison's Anæmia?

Had he left it at that, Addison would have gone down in history not only as having given a clear description of Addison's disease and associated it with deficiency of the function of the adrenal glands, but also as having given a lucid account of Addison's anæmia—indeed it was probably the first accurate record of this disease, though the case described in 1824 by James Scarth Combe [30], a young practitioner of Leith, also deserves consideration. Robb-Smith [31] is inclined to think that it was a genuine case of pernicious anæmia, and feels in any case that Combe deserves full credit for a very clear account of an idiopathic anæmia. Sir Lionel Whitby [32], in his Addison Lecture delivered in March this year, discusses Combe's case and expresses the opinion that Addison's description is far superior to that of Combe whose patient had indeed a severe anæmia but with no convincing features of Addisonian anæmia. The other claimant to the discovery of pernicious anæmia is Professor Anton Biermer [33] of Zurich who in 1872 gave a full account, based on a study of fifteen cases, of "progressive pernicious anæmia". Suffice it to say that here again these two hæmatological experts disagree. Robb-Smith, however, attributes the final discovery to Paul Ehrlich [34] who established modern hæmatology by his work on aniline dyes which enabled him to distinguish three types of nucleated red cells—the megaloblast, the normoblast and the microblast. He was the first, therefore, to introduce an objective criterion for the diagnosis of pernicious anæmia by classifying it as a megaloblastic anæmia. This, however, brings the discovery of "Addisonian" anæmia forward to the year 1880. Addison, indeed, has been bitterly criticized, for instance by Cecilia Mettler [35] in her "History of Medicine", for using no hæmatological methods, but Robb-Smith points out that in 1843, when Addison was first beginning to teach his students at Guy's about an "idiopathic" form of anæmia not due to nutritional, cachectic or other causes, no method of numeration of red cells had been devised.

If, therefore, Addison in his Address to the South London Medical Society in 1849 had merely contented himself with a straightforward clinical description of pernicious anæmia, he might have gone down to posterity as the man who, by clear-sighted and careful clinical observation, had discovered Addison's anæmia. On the other hand he might never have discovered Addison's disease, for though he had been able to make a post-mortem examination on only three of his series of cases of anæmia he found a diseased condition of the suprarenal capsules in all of them. He admitted that this might be a coincidence—as indeed it must have been if they were cases of pernicious anæmia—but thought not. On the contrary, he could not help entertaining a very strong impression that these hitherto mysterious bodies—the suprarenal capsules—may be either directly or indirectly concerned in sanguinification; and that a diseased condition of them, functional or structural, may interfere with the proper elaboration of the body generally, or of the red particles more especially. And so he who was so especially interested in the colour of the skin became "suprarenal-minded". It is quite clear that he had no thought of Addison's disease in 1849. He certainly stands convicted of introducing the red herring of the diseased suprarenals, but the cases he described in 1849 were classical cases of idiopathic anæmia.

The Concept of Addison's Disease

In his 1855 Monograph he describes Addison's disease with its characteristic dark pigmentation in contrast to the "blanched, smooth and waxy appearance of the whole surface of the body which bears some resemblance to a bad wax figure".

It seems to me, therefore, that Addison, the dermatologist and general physician, drew attention to idiopathic (Addisonian) anæmia, and among the series of cases he studied he found diseased suprarenals in the only three in which he managed to perform a post-mortem examination. He therefore believed that he had discovered some function for the hitherto altogether mysterious capsules—that they are concerned in sanguinification. Later he became interested in a condition associated with a darker pigmentation of the skin in which again he found disease of the suprarenals at autopsy. This time he was right for the condition he described with dark pigmentation is in fact Addison's disease and is due to destruction of the suprarenal glands.

Addison's Career

Addison was essentially parochial, the devoted adopted son and loyal and distinguished servant of Guy's. He received his chief education at Newcastle-upon-Tyne where he

accumulated a scholarly knowledge of Latin which he spoke and wrote fluently. He took his M.D. at Edinburgh in 1815 and then came to London at the age of 22 to enter upon the practice of his profession. For a time he was House Surgeon at the Lock Hospital (the subject of his M.D. thesis was "De Syphilide et Hydrargyro") and in 1817 he paid his fees to become a "perpetual Physician's pupil" at Guy's. In 1819 he was appointed Physician to the Carey Street Dispensary in succession to Richard Bright. At Guy's by 1820 he had attracted the attention of Mr. Benjamin Harrison, junior, then in the twenty-third year of his reign as the all-powerful Treasurer of the Hospital. Harrison, personally, was largely responsible for having Addison appointed to the Staff. Addison lost little time in setting to work upon his great career as a teacher, for the new Guy's Hospital Medical School was founded the year after Addison was appointed to the Staff, and he, Bright and Hodgkin were largely responsible for building up its great reputation, for Addison was primarily a great clinical teacher. To illustrate this I quote from Wilks and Bettany's "Biographical History of Guy's Hospital" (1892):

> "Upon the writings just mentioned will Addison's name in future years rest, but during his lifetime they contributed little to the reputation which he then enjoyed. This, which was very great, was entirely owing to the personal influence which he exerted on his pupils and others who came in contact with him. His original work on chest disease did not appeal to students, and his memoir on suprarenal disease did not appear until near the close of his career. The personal power which he possessed was the secret of his position, much superior to what Bright could ever claim, and equal, if not greater, than that of Sir Astley Cooper. For many years he was the leading light of Guy's, so that every Guy's man during the thirty or forty years of his teaching, was a disciple of Addison, holding his name in the greatest reverence, and regarding his authority as the best guide in the practice of the profession. Addison was not learned in the history of medicine; whatever he said was his own, and his sayings were eminently practical. He was dogmatic in his teaching, and thus the pupils accepted as pure gospel every word which flowed from his lips. The force of his words was enhanced by his mode of delivery and by the presence of the man himself. Addison was of good height and well made, stood erect, with coat buttoned up very high, over which hung his guard and eyeglass. He wore a black stock with scarcely visible shirt collar, and this further elevated his head. He had a well-proportioned, good head, with dark hair and side whiskers, large bushy eyebrows and smallish dark eyes, nose thick, as were also the lips which enclosed his firmly knit mouth. His features were not refined, but belonged to a powerful mind, and showed no trace of any kind of sentiment. His penetrating glance seemed to look through you, and his whole demeanour was that of a leader of men, enhanced by his somewhat martial attitude."

FIG. 1.—Thomas Addison. By kind permission, Guy's Hospital.

Addison as a Chest Physician

Despite the fame that has come to him as the founder of Endocrinology, the discoverer of idiopathic anæmia and as a dermatologist, the principal interest throughout his life was in diseases of the chest. He was an indefatigable morbid anatomist and lost no opportunity of dissecting the body both in the dead-house and in his own home, and this led him to describe with accuracy, in the light of modern teaching, the anatomy of the pulmonary vessels, and to deny the existence of the so-called "parenchyma" of the lung which was considered to be the site of pneumonia [36], and to teach that pneumonia was in fact an inflammation of the air cells [37]. Another observation which Addison's zealous studies of morbid anatomy disclosed was that the presence of tubercles was not essential in the condition known then as "phthisis" [38], the signs and symptoms of which could be produced by diseases other than tuberculosis, such for instance as pneumonia or lung abscess, which might be fatal even though no tubercles were present. He was an ardent admirer of Laennec who had invented the stethoscope in 1819, nevertheless he tilts mildly at the "stethoscopists" and emphasizes that of "all the symptoms of pneumonia, the most constant and conclusive, in a diagnostic point of view, is the pungent heat of the skin". In addition to his articles on chest disease he also wrote papers on Fatty Degeneration of Liver, Disorders of Females connected with Uterine Irritation, a Case of Ovarian Dropsy, Disorders of the Brain connected with Diseased Kidneys, and the Influence of Electricity as a Remedy in Certain Convulsive and Spasmodic Diseases. Addison, in fact, was the first to suggest the use of static electricity in the treatment of certain spastic diseases. He also wrote with his surgical colleague at Guy's, John Morgan [39], the first book on poisons, in 1829, in the English language.

Addison's Character

Addison was a lonely figure and a bachelor until he was 52 years old when he married a widow with two children all of whom survived him. He devoted himself to Guy's where he reigned supreme. He held no office in the Royal College of Physicians, he was not elected a Fellow of the Royal Society, and he was not created a baronet, like Astley Cooper, Gull and Wilks. He was scrupulously honest, scientifically incapable of saying or indeed hearing a harsh word against a colleague; he was secretively generous to young and struggling disciples. His Boswell was Samuel Wilks, that "publicity agent of diffident Guy's physicians" as Robb-Smith aptly calls him—for it was Wilks who, being the first to recognize the clinical feature of Hodgkin's disease, found that Hodgkin had previously described its pathology, and therefore generously applied Hodgkin's rather than his own name to the eponymous title we know to-day. But Wilks was more than a mere Boswell. He was a student sitting at the feet of Addison in 1849 when the South London Medical Society paper was read, and he undoubtedly goaded him on to write the Monograph. It was he who knew him best, and it was he, in Wilks and Bettany (1892), who tells us how his students worshipped him, but feared rather than loved him; how his practice but slowly advanced so that he remarked that he depended on the profession for his patients, for the public would have let him starve (nevertheless he died worth £60,000); how he was for ever trying to discover the derangement in a piece of machinery, rather than regarding his patient as a suffering sensitive human being who has got out of the lines of health. It was Wilks who tells of his awful fits of despondency associated with some fearful circumstances which made him wonder that he was still alive to tell the tale, and how he walked the streets at night to get rid of his depression; how a certain bluntness of expression, combined with the dignity of his bearing and an appearance of haughtiness, would make him seem unapproachable, though in fact it was, as Addison himself declared, a cloak for his nervousness. He was obsessional, and would ponder into the small hours over a case in the wards, dress himself, take a cab to the hospital and surprise the Ward Sister by appearing in the middle of the night to examine a patient for a hernia, because he had forgotten to do so on his afternoon round. Seldom did he prescribe, for he was too honest to have much respect for the therapeutics of those times, but diagnosis was for him something that must be pursued to the point of exhaustion, and he frequently exhausted both his students and his patient darting from one side of the bed to the other because he was deaf in one ear. His attacks of melancholy became more constant, and he began to suspect that his younger colleagues and particularly Gull, wished to deprive him of his position. Sir Hermann Weber [40], the father of Dr. Parkes Weber, and an intimate friend of Addison says that this led him to attempt to commit suicide in 1858 by throwing himself from a window, though guarded by two attendants. Incidentally, Sir Hermann Weber gives it as his opinion that Addison had as much to do with the discovery of Bright's disease as Richard Bright did. In 1860 Addison resigned from Guy's, and in reply to an expression of condolence from the pupils of the hospital, he wrote this letter to their spokesman:

March 17th 1860.

My Dear Sir,

A considerable break-down in my health has scared me from the anxieties, responsibilities, and excitement of the profession: whether temporarily or permanently cannot yet be determined; but, whatever may be the issue, be assured that nothing was better calculated to soothe me than the kind interest manifested by the pupils of Guy's Hospital during the many trying years devoted to that institution.

I can truly affirm that I have ever found my best support and encouragement in the generous gratitude and affectionate attachment, as well as my proudest reflections, in the honourable and exemplary conduct of its pupils. Present my sincere regards and best wishes to every one of them, and believe me,

Yours truly and affectionately,
THOMAS ADDISON.

A resolution of the General Court of Governors of the Hospital recorded at length its appreciation of Addison's services. Addison alone joined Astley Cooper in receiving so full a tribute of gratitude.

He retired to Brighton, and very shortly after, as the Obituary notice in the *Medical Times and Gazette* [41] rather enigmatically puts it, "he settled down into a state of melancholy from which nothing could arouse him, and closed his career last Friday week" (that is, Friday, June 29, 1860, a few months after the death of Richard Bright).

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Section of Ophthalmology

President—HUMPHREY NEAME, F.R.C.S.

[*June* 9, 1955]

Intracranial Aneurysm.—J. R. WHEELER, M.B., F.R.C.S.Ed.

Woman, aged 53. Examined May 17, 1954.

History.—Four days before had sudden severe pain like an explosion inside the head. Pain rapidly spread over the head generally to neck and shoulders. Did not faint but felt sick and had to lie down at once. In about twenty minutes when pain moderated a little and she became more composed she found she could not see at all with her left eye. Headache, soreness at back of neck and amaurosis of left eye persisted, the headache gradually lessening during the subsequent week. Right eye normal. No spread of pain to any of the divisions of left V cranial nerve during the attack.

Previous history.—Examined by me on September 8, 1953. Left eye normal apart from small refractive error. Six months later, i.e. about two months prior to above attack, noticed when looking at objects with left eye could only see the lower half: left superior hemianopic defect—but did not report this observation to her doctor.

Only complaint now is loss of vision in left eye—headache gone.

On examination.—Eyes: Right—Vision=6/6. Media clear, fundus normal and visual field full. Left—Vision=no light perception—pupil, no direct reaction to light but reacts consensually. Media clear. Fundus, slight pallor of disc and vessels somewhat contracted.

C.N.S.: Clinical examination, apart from a ? slight left facial weakness, was normal.

Diagnosis.—The history of an acute episode suggests a ruptured intracranial aneurysm. The aneurysms arising in the region of the circle of Willis can be divided clinically into two main groups: (*a*) Subclinoid, arising from the internal carotid in the cavernous sinus before it has pierced the dura; (*b*) Supraclinoid, arising from the carotid or its branches after it has pierced the dura.

To get precise information on an aneurysm one needs an angiograph, but this entails definite risks which may be fatal. While an angiograph should be done as early as possible it is well to remember that following the initial rupture there is an interim period varying in length from case to case when the cerebral circulation is labouring under duress. Watchful conservation is the wisest course until the systemic blood pressure has returned to normal for a few days and any clouding of consciousness considerably diminished. To complete the diagnosis and carry out the necessary treatment this case was handed over to the care of Mr. C. A. Calvert, senior neurosurgeon at the Royal Victoria Hospital, Belfast.

EEG: Probably a normal record. No abnormal waves or focus seen.

Angiograph: There is a very large aneurysmal dilation of the upper limb of the carotid siphon well below the bifurcation (Fig. 1). The oblique view shows that the aneurysm originates from the carotid by a small neck and antero-medially to the vessel. There is a good cross circulation on compression of right carotid artery (Fig. 2).

Treatment.—June 11, 1954: Ligation in continuity of left common carotid artery completed at the end of an hour as there were no neurological signs. The procedure caused a bitemporal headache and discomfort about nasopharynx for a few days. For next few weeks patient felt weak and easily tired but at the end of a month was back to normal. There was no return of vision to left eye.

August 15, 1954: Ligation of left internal carotid artery.

One year after the acute episode the patient's general health is good, but of course the left eye is blind.

Comment.—Six months ago my neurosurgical colleague, Mr. C. A. Calvert, read a paper on "Ruptured intracranial saccular aneurysms" to the Society of British Neurosurgical Surgeons. 117 cases of verified subarachnoid hæmorrhages were reviewed. It was found that 22% had a III nerve lesion, 6% a VI nerve lesion, 2% were blind in one eye while 5% had either a subhyaloid hæmorrhage or papillœdema.

In these comparatively common and highly dangerous vascular lesions one must protect the patient as soon as possible against the hazard of a second hæmorrhage which may overwhelm the cerebral mechanism.

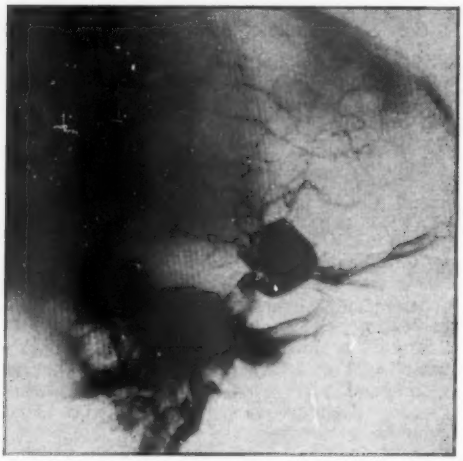

FIG. 1.—Lateral view showing aneurysmal dilatation of the siphon.

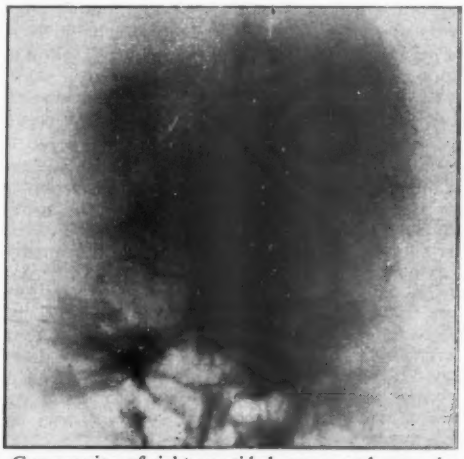

FIG. 2.—Compression of right carotid shows a good cross circulation.

To operate logically one must localize the lesion, so angiography was done in 104 cases, and 4 deaths occurred as a result of the procedure. In only 79 cases was the aneurysm revealed. All but one of these cases belonged to the carotid system. The distribution of the aneurysms was as follows:

33 Supraclinoid carotid siphon of which 17 had III nerve and 3 VI nerve lesions, while 2 were blind in one eye.

25 Middle cerebral of which 3 had III nerve lesions while 6 showed either papillœdema or a subhyaloid hæmorrhage.

14 Anterior cerebral or anterior communicating of which one had III and one VI nerve lesion, while 7 showed papillœdema or subhyaloid hæmorrhage.

3 Distal portion anterior cerebral.

3 Bifurcation internal carotid.

1 Posterior cerebral.

The practice in the Belfast school is to employ ligation of the carotid vessels in the neck for aneurysms on the supraclinoid portion of the internal carotid and to have recourse to a direct intracranial attack on those situated more peripherally, as on the anterior part of

the circle of Willis and its branches or the middle cerebral artery. This policy is adopted on the assumption that while carotid occlusion would result in a permanent reduction of intra-arterial pressure and expansile thrust of blood as high as the internal carotid bifurcation it would not be likely to have more than a temporary effect on the pressures in the circle of Willis and its branches. Also it is technically simpler and various tests give some guide (not infallible) as to safety. In the 117 cases under review 57 had a definite operative procedure. Of these a direct attack was made on the aneurysm in 31 patients and there were 6 deaths. 26 cases of supraclinoid internal carotid aneurysms were treated by ligation in the neck and there were 2 deaths. The pre-operative neurological defect of this latter group included 14 III nerve lesions of which 9 made a complete recovery. 3 are blind in one eye and another has very poor vision. 4 cases developed hemiplegia but made a good recovery. 20 patients show no residual disability. There have been no recurrences.

Commentary.—The advance of angiography shows that supraclinoid aneurysms produce considerably more oculo-motor lesions than was previously realized. In the cases reviewed 25% showed some oculo-motor lesion while there were only 19% visual defects.

In cases which survive the original vascular episode the neurosurgeon can offer the patient quite a good prognosis by operative interference.

Cataracts Associated with Neurodermatitis. Their Treatment and Complications

By M. J. Gilkes, M.B., F.R.C.S.

Of a number of types of association of cataract with a dermatosis which have come to be recognized since the first report by Rothmund in 1868 there have now been isolated several distinct classifications, comprising poikiloderma with cataracts (Rothmund's syndrome), scleroderma with cataracts (Werner's syndrome), neurodermatitis, both local and general, and a lesser group, where the association is much less strong, including Darier's disease, erythema exudativa and Raynaud's disease among others.

Neurodermatitis forms the largest of these, being, when unassociated with lens changes, a not uncommon dermatological condition. However, it presents to the enquirer a most complicated aspect owing to the variety of nomenclature with which the condition has been endowed: As for example, atopic eczema, allergic eczema, anaphylactoid dermatitis, prurigo diathésique and lichen simplex chronicus, not to mention a number of eponymous terms of which perhaps the most widely used is Besnier's prurigo.

So varied a terminology leads one to expect a condition of marked pleomorphism but although this is indeed the case there are certain basic characteristics which indicate a diagnosis of neurodermatitis.

It is almost the rule to find a family history of isolated cases of asthma, eczema, allergy or a combination of these; although there is rarely a direct familial inheritance. The patients themselves may be asthmatic and subject to allergic manifestations and often present evidence of psychical instability.

The skin lesions, which may be either local or general and in some cases interchangeable, are characterized by the development, usually in the first two decades, of a thickening and pallor of the epidermis, associated often with xeroderma, which affects mainly the face and the limb flexures. This may spread, in the generalized form, to the rest of the skin, usually in association with a secondary eczematization. The lesions are remissive and relapsing in nature, relapses commonly being associated with the onset of some environmental stress. Pruritis with almost uncontrollable paroxysmal scratching is the rule and results in the typically scarred character of the rash seen in the patients shown.

The feel and appearance of the skin of these cases is quite characteristic and has been aptly described by Ingram (1955) as possessing in its thickening, lack of suppleness and exaggerated lines, all the characters of an animal hide.

Three types of ophthalmic complications are found in this condition.

Firstly, the skin of the lids is involved in the general thickening, dryness, and intermittent eczema of the face.

Secondly, cataracts occur, of characteristically sudden onset, sometimes proceeding to complete maturity within a few weeks. These may be classified in two main types: (1) Posterior and anterior cortical subcapsular opacities which coalesce and spread to form a homogeneous mature cataract. (2) An anterior subcapsular opacity, often shield-shaped, develops followed by a thickening and wrinkling of the anterior capsule which later spreads to the rest of the lens. Maturity may take considerably longer to develop in this type.

A combination of both types may also occur. In either case the onset may be at any age, but appears commonest in the third decade and usually post-dates the onset of the skin lesions by a decade or more.

Thirdly, retinal detachments have been rarely reported in association with this condition (Balyeat, 1937; Mylius, 1949).

Although the association of cataract with this condition is so definite and indeed the appearance of the scutellar opacity might almost be held to be pathognomonic of neurodermatitis, several interesting facts come to light when one considers the incidence of cataract in this condition.

Various authorities give figures ranging from 2–20% of all cases of neurodermatitis as having cataract. Cowan and Klauder in 1950 gave an incidence of 8%, while a recent paper by Ingram (1955) gave 16%. In discussion various dermatologists have held both these figures to be high.

In Cowan and Klauder's series a third of the cases were found to be unilateral and in 2 out of the 10 cases on which the present paper is based the lens changes were unilateral. There will be cause to return to this later.

With regard to a possible association between the severity of the skin lesion, and the onset of lens changes, the literature is again at variance, some authorities holding that cataracts only occur in cases with severe generalized neurodermatitis, while Milner in 1941 felt that cataracts were rare in what he termed generalized allergic eczema.

In the present series 6 cases might be held to have severe and at times generalized neurodermatitis while the remaining cases at the time of onset of the cataracts had relatively mild skin changes.

Bearing in mind the likelihood that a quiescent skin may be activated by the mental stress of failing vision, one is tempted to feel that any increased association of cataract with the generalized form of the disease may be as much *post* as *propter hoc*.

The following cases may be taken as representing quite typical examples of this condition.

Case I.—D. P., male, aged 23.

1951, attended hospital, complaining of loss of vision. Rash on face and arms and legs since entry to Army, aged 18. Discharged after three months, admitted to sanatorium 1947: Pulmonary tuberculosis. Recurrence of rash at this time. Skin treated with X-rays in 1951.

Family history.—Mother had eczema until aged 40. No cataract in family. 3 sisters healthy.

On examination.—R. 6/18. L. H.M. R. Central subcapsular lens opacities. L. Mature lens opacities with anterior subcapsular opacities. Typical localized skin changes.

Case II.—J. S., female, aged 27.

Aged 15, onset of skin condition of face and hands. Domestic stress at home at this time.

Aged 19, in association with stress of her prospective marriage recurrence of skin condition and onset of various episodes of an allergic character. The condition became generalized and finally a leucotomy was performed for her attacks of compulsive scratching.

Aged 23, R. vision became blurred.

Aged 24, L. vision blurred suddenly.

Family history.—Mother had allergic history. No cataracts.

On examination.—R. H.M. L. H.M. R.L. Mature homogenous cataracts. Severe generalized neurodermatitis and secondary eczema.

Case III.—J. D., male, aged 22.

1951, attended hospital, complaining of failing vision. Skin condition present since birth. Asthmatical. Allergic to eggs and nut oil. Recurrent exacerbations of rash in association with nervous stress.

Family history.—2 brothers with eczema and asthma. Father has a dry skin. Maternal grandmother had asthma. No cataracts.

On examination.—1951: R. 6/6. L. 6/6. R. Lens clear. L. Anterior subcapsular opacity. 1954: R. 6/60. L. 6/18. Marked opacities in both lenses with anterior shield opacities.

Case IV.—J. H., female, aged 17½. 1955, attended hospital, complaining of failing vision L.E. two years. Slight rash of face and flexures for years. No asthma.

Family history.—None, no cataracts.

On examination.—R. 6/6. Lens clear. L. H.M. Mature cataract.

Case V.—M. C., female, aged 38. 1954, aged 37, attended hospital, complaining of loss of R. vision. Rash of face and limbs for ten years. No asthma. Possible allergy to onions.

Family history.—None, no cataracts.

On examination.—R. P.L. Good projection. L. 6/6. Lens clear. Mature cataract. Skin changes on face and hands.

Four other cases all present the same basic pattern.

Now, although the basic pattern of these cases may at first be clear, their ætiology is undoubtedly a matter for conjecture. This is reflected in the literature which is replete with a terminology of allergy, atopy and endocrine imbalance, which when examined leaves little more than a name.

However, the point is well made by Ingram when he states that the skin lesions are

characteristically epidermal and ectodermal, as compared with the dermal and mesodermal nature of a simple eczema, and that the involvement of ectodermal eye structures is fully consistent with the rest of the condition.

Recently, Russell and Last (1955) have suggested that a proportion of these cases have abnormal electroencephalograms of a type found in epilepsy and that the lesions might be explicable in terms of what could be called a dermato-epilepsy.

Finally, there is little doubt that through the ectodermal nervous system there is a direct psychosomatic influence on both the commencement and continuance of the skin lesions.

From the ophthalmic point of view, however, none of these views come near to explaining the relatively low incidence of cataract and its not infrequent unilaterality in this disease.

If an ectodermotoxic factor is held to be responsible one would expect a much greater incidence of cataract and bilaterality. One is tempted to consider that the lens changes are a concomitant of the skin condition rather than a sequel and this thought may be strengthened by a consideration of the following 3 cases:

Case VI.—D. F., female, aged 43.

August 1954, attended hospital, complaining of failing vision both eyes. In September 1953, R. 6/6. L. 6/9.

On examination.—R. 6/18. L. 6/36. Bilateral posterior cortical lens changes. No family history. Seven years ago following a severe shock developed a rash on chest and back. This was diagnosed as a "nerve rash" when she attended for treatment. Simultaneously she developed a severe allergy to fish which is still present. The rash disappeared after some months. By March 1955 her vision was R. C.F. L. 6/36. The R. cataract was almost completely mature.

Case VII.—K. B., female, aged 32.

1949, attended hospital, complaining of blurred R. vision for three months.

Family history.—Brother, now deceased, had a scaly rash. Two stepbrothers with asthma, no cataracts. Patient is asthmatical and subject to hay-fever. Never had any rash. Pulmonary tuberculosis 1946. No evidence of endocrine disorder.

On examination.—1949: R. 6/18. L. 6/12. R.L. Lens opacities, posterior cortical in character with ring-shaped anterior capsular opacity.

October 1951: R. 2/60. L. 6/36.

Case VIII.—J. S. male, aged 51.

Attended hospital 1952, aged 48. Complained of failing vision both eyes. 1930, at time of marriage, developed skin rash involving flexures, disappeared after few months. Never any rash since. No asthma.

Family history.—Mother, hay-fever. Father, cataract aged 60. Eldest sister with asthma.

On examination.—R. 6/12. L. 6/60. Indefinite cortical opacities R.L. No rash.

Now in all these cases we find cataracts of a pre-senile character with no definite ætiological association, but with a strong asthma-allergy background. Further, the morphology of the cataracts is suggestively similar to that described in neurodermatitis. Yet only in one case was there a rash even vaguely suggestive of that typically found. There would appear to be some agency at work here which although separate from the epidermotoxic factor of neurodermatitis is probably identical with that causing the cataracts found inconstantly in that condition.

It would appear that a thorough survey of not only the dermatological, but also the asthma-allergy history of any case of pre-senile cataract of unknown ætiology, might well be of assistance in helping to place the case in the correct classification. With regard to the ætiology, however, this leaves one little further on, and the views of Nordmann in regard to this matter are perhaps worthy of repetition: . . . "It is certain that no evidence exists of any change on the part of the ciliary epithelial cells, the aqueous, or of the lens capsule. Besides one knows that the lens capsule of the adult is impermeable to antibodies. Also cutaneous tests made with aqueous humour or with lens substance, in these cases, have always been negative. In consequence one is led to conclude that the allergic origin of atopic cataract is far from having been demonstrated."

The operative treatment of the cataracts in these cases has been dismissed by many authors, amongst them Kirby (1950) and Bellows (1944), as offering little difficulty, and this statement has been copied widely.

There is, however, little doubt that the more severe of these cases offer considerable problems when treatment comes to be considered.

Pre-operatively, several factors will have to be considered. Firstly, the skin lesions offer a perfect niche for organisms which are commonly insensitive to all or most antibiotics, and the procurement of a sterile pre-operative culture may be a matter for considerable patience and therapeutic ingenuity.

Secondly, in many patients there is a tendency to develop sensitivities to medicaments, while the psychical stress of an impending operation may also result in a severe exacerbation of the skin condition sufficient to enforce postponement. Accordingly it is often advisable

to proceed by stealth, taking the patient into the theatre without prior notice. In one of the cases reported even this did not suffice, as within a few minutes of his being placed on the table a severe relapse in his skin condition occurred.

The actual technique to be employed again requires considerable thought. Although the patients are usually young, Brunsting (1936) states that nuclear sclerosis may be present making linear extraction a matter of some difficulty. However, this difficulty was not encountered in the present series and the opposite is stated by some authorities to be the case.

One of the most important factors to be taken into consideration is the possibility of the development of a phaco-anaphylactic sensitivity in bilateral cases, resulting in a severe uveitis in the second eye following extracapsular extractions separated by a period of more than two or three weeks. Duke-Elder and Goldsmith (1955) have in fact suggested that in cases of this type arrangements should be made to operate on the second eye within three weeks to avoid the severe and destructive uveitis which may otherwise supervene. This might well be avoided by using the intracapsular method. On general grounds of age, however, this is likely to be beset with difficulties, and specifically might be regarded as undesirable owing to the known liability of these patients to retinal detachments. There appears to have been little work done on desensitization with lens protein injections in these cases.

The post-operative course of these cases is also beset with difficulties, the least of which is a fairly general relapse of the skin condition. Apart from this severe hypopyon uveitis, retinal detachments and retinal hæmorrhages have been noted.

Coles and Laval (1952), in a summary of all the reported cases, comprising 63 cases in all, found 36% of unfavourable results, with retinal detachments in 22%. Amongst a series of 11 cases collected by me the operative results have been rather better but still give grounds for caution. Of 16 eyes operated on, 11 gave no cause for apprehension, but there was one detachment, one phaco-anaphylactic uveitis, one phthisis bulbi, one recurrent hypopyon iritis resulting later in a 6/6 eye, and one eye with a drawn-up iris, although with good visual acuity; a 31% complication rate and 18% loss rate, which does not take into account the very severe skin complications following operation which occurred in several of the cases.

My thanks are due to Mr. A. G. Leigh for permission to show two of his cases.

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Mr. L. H. Savin, speaking on Mr. Gilkes's paper, said that he had had a patient with the same condition of cataracts associated with neurodermatitis. She also suffered severely from asthma. One eye was completely blind with cataract and retinal detachment. The other eye had a cataract on which he operated, and that was successful. She was still working as a bank clerk. He wondered whether there was some friability of the retina which predisposed to retinal detachment. Was there any record of how these cases responded to surgery?

Mr. Gilkes, in reply, said that it was interesting to hear of yet another case where an apparently spontaneous detachment was associated with neurodermatitis. The underlying agent might involve any of the ectodermal eye structures. The response of these cases of detachment to surgery appeared to be poor.

Section of Radiology

President—J. F. BROMLEY, O.B.E., F.R.C.P.

[*April* 15, 1955]

Œsophageal "Spasm" in Infancy

By ROY ASTLEY, M.B., M.R.C.S., D.M.R.

The Children's Hospital, Birmingham

IN this short communication I wish to draw attention to certain conditions of temporary and presumably spastic obstruction in the lower portion of the infant's œsophagus.

For convenience two grades of obstruction may be considered: firstly, an œsophageal blockage that is initially complete; secondly, one that is partial from the outset.

The first type I have only seen in the first few weeks of life. During a barium examination there is seen to be a complete hold-up just above the diaphragm. The œsophagus remains barium-filled down to a point of termination from which one or more tiny irregular processes may appear to extend to a slightly lower level. The final 1 to 2 cm. of the gullet remain empty.

After a few minutes the obstruction may disappear suddenly. The disappearance may be complete or partial, with an intermittent or irregular trickle of barium passing through the last centimetre or so into the stomach. The passage of an œsophageal tube has been seen to initiate this change.

More often, the obstruction is of the second grade: a partial one from the outset. There is a hold-up at the same level, 1 to 2 cm. above the diaphragm; below this the barium passes as an intermittent jet and the lumen may appear irregularly narrowed.

In one baby who gave this fluoroscopic picture with an initial obstruction of the complete type, no cause for the spasm was ever discovered. Subsequent progress and further X-ray examinations were normal. In all other instances the temporary obstruction, whether complete or partial, has proved to be a manifestation of gastro-œsophageal incompetence. The site of blockage has corresponded with the cardia and the segment of gullet below it has proved to be a small portion of intrathoracic stomach. On some occasions it has been possible to prove this at the same X-ray examination once the spasm has relaxed; in other children, further examinations have been necessary to clinch the diagnosis.

ILLUSTRATIVE CASES

Case I.—Male, aged 6 days. He was a first child, normally delivered at full term, birth weight 6 lb. 5 oz. His condition after birth was good but he vomited after his first and all subsequent feeds. There was no blood or bile in the vomitus and he passed meconium normally. On the day of admission to hospital he had vomited twice and became temporarily cyanosed after the second occasion. On examination he was a lusty baby with no abnormal physical signs.

FIG. 1 (*Case I*).—Temporary obstruction in the lower œsophagus for which no cause could be discovered.

At fluoroscopy, there was a normal distribution of alimentary gas. Thin barium was completely obstructed about 2 cm. above the diaphragm.

At first there was a perfectly rounded œsophageal termination, with a hold-up of at least five minutes. Then a tiny tail of barium was seen to protrude downwards. Eventually three little tails could be identified but still no barium passed (Fig. 1). At this stage, about ten minutes after the initial giving of the barium, a soft rubber catheter was passed through the mouth and easily reached the abdomen. Immediately the obstruction disappeared and barium passed down into the stomach. The examination was concluded at this stage.

The baby was tube-fed for the next few days and then by bottle, without further vomiting. A repeat barium meal, fourteen days after the first, was completely normal and so was his further clinical progress. At 13 months of age he was a fit, asymptomatic child and another barium examination was completely negative.

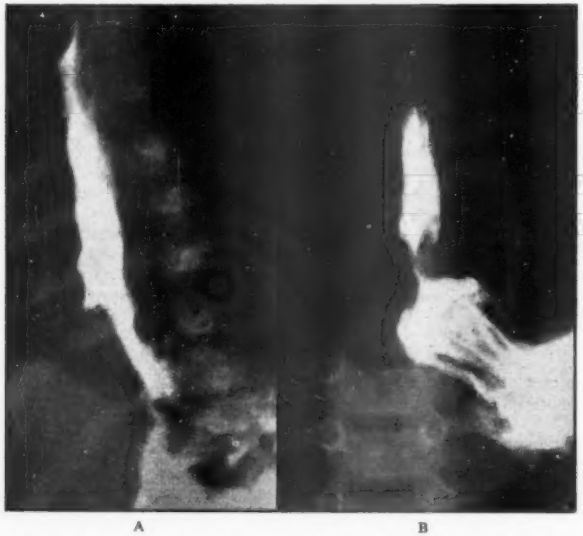
Comment.—This was the baby mentioned previously as the sole example of a temporary obstruction for which no cause was found.

Case II.—Male, aged 1 month; a history of vomiting since birth, with blood streaking of the vomitus on several occasions. At fluoroscopy, the first mouthfuls of barium were obstructed about 2 cm. above the diaphragm where the œsophagus showed a pointed, rather irregular termination. After two to three minutes of complete hold-up the barium trickled into the stomach through a narrow, irregular channel. More barium was given and it continued to pass through the apparent narrowing. Eventually enough had reached the stomach for the application of manœuvres to test the competence of the gastro-œsophageal valve mechanism. Abdominal pressure produced reflux which distended the previously narrowed area and revealed that it was really wider than the œsophagus higher up and that in fact it was a small loculus of stomach above the diaphragm. The hiatus was wide and there was a loss of the normal gastro-œsophageal obliquity. Once the initial hold-up at the level of the intrathoracic cardia had been overcome there was no further obstruction and reflux continued freely.

The child was treated by constant nursing in the erect position, with a decrease in the amount of vomiting. A month later another barium swallow confirmed the gastro-œsophageal incompetence and the thoracic stomach but there was no obstructive element. Another month later vomiting was only occasional; the X-ray findings were unchanged.

Comment.—In this instance a spasm at the level of the elevated cardia (secondary to œsophagitis) was presumably the cause of the temporary obstruction at the initial examination. This permitted only a trickle to pass down amongst the mucosal folds of the thoracic stomach, which therefore appeared as an irregularly narrowed area.

Case III.—Male, aged 3 months; he had vomited persistently since about 3 weeks of age, with blood in the vomitus on several occasions. During the barium swallow (Fig. 2A) there was a partial



A B

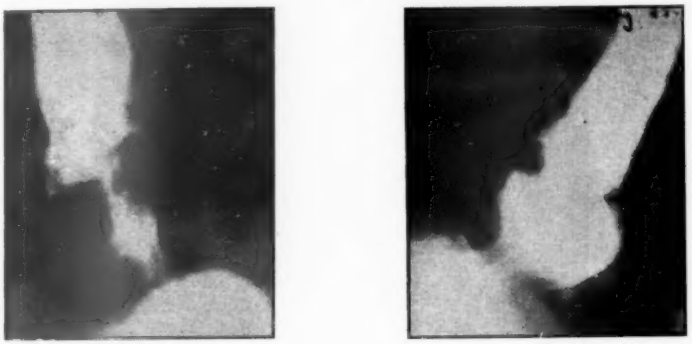
FIG. 2 (*Case III*).—A, Temporary partial obstruction in the lower œsophagus with an apparent irregular narrowing below it. B, The "narrowed" area is really a loculus of stomach above the diaphragm.

hold-up about 2 cm. above the diaphragm. Above this point the lumen had slight irregularities of contour, attributable to œsophagitis; below, the barium passed through an apparently irregular narrowed channel into the stomach. Once enough barium had reached the stomach, abdominal pressure produced ready reflux; immediately it became apparent that the lower portion of the gullet was not narrowed but was really expanded and was, in fact, part of the stomach that was situated above the diaphragm. Once reflux had been initiated it continued and there was no longer any obstructive effect at the intrathoracic cardia.

The child was treated by erect nursing with considerable improvement and after two weeks vomiting had ceased. During the next year there were intermittent relapses but by the age of 2½ years he had not vomited at all for twelve months; he had no dysphagia or other symptoms and was very well. During this period he had several X-ray examinations which showed little change (Fig. 2B). There was gastro-œsophageal incompetence with stomach extending above the diaphragm but no obstructive element. At 2½ years old reflux was readily obtained from the abdominal to the thoracic stomach but it was only occasional to the œsophagus.

Comment.—Similar to Case II but a more partial type of initial temporary obstruction associated with a partial thoracic stomach.

Case IV.—Female, aged 1 month; she had vomited practically every feed from birth, with blood in the vomitus on one occasion. She was dehydrated and very much underweight. At the outset of the X-ray examination there was a hold-up above the level of the diaphragm and the barium passed intermittently through the last couple of centimetres into the stomach (Fig. 3A). Once reflux could

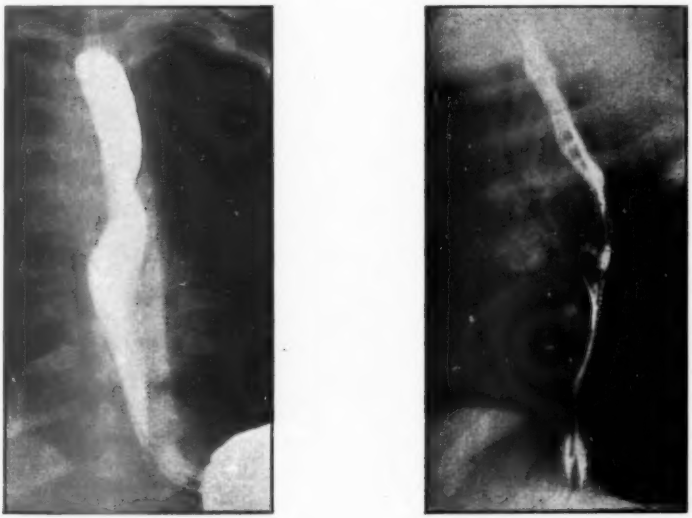


A B

FIG. 3 (*Case IV*).—A, Temporary partial obstruction in the lower œsophagus. B, The spasm has relaxed and a loculus of thoracic stomach is revealed.

be demonstrated, however, the obstruction disappeared and it was apparent that the area of previous narrowing was really thoracic stomach (Fig. 3B). The barium had passed as a jet because it was emerging from a temporarily, and presumably spastically, obstructed gastro-œsophageal junction. In this instance a cine-film was taken with the aid of image amplification and demonstrated the intermittent jet-like passage of the barium; the terminal portion of the film, taken at a later examination when there was no obstructive element, demonstrated the stomach above the diaphragm.

Case V.—Female, aged 1 year, with stridor due to a foregut duplication cyst of the bronchogenic type. It was obstructing the left bronchus and producing an obstructive emphysema of the left lung. The œsophagus was deviated posteriorly and to the left around the cyst while the trachea was narrowed and displaced anteriorly (Fig 4A, B). At thoracotomy, Mr. A. L. d'Abreu dissected out

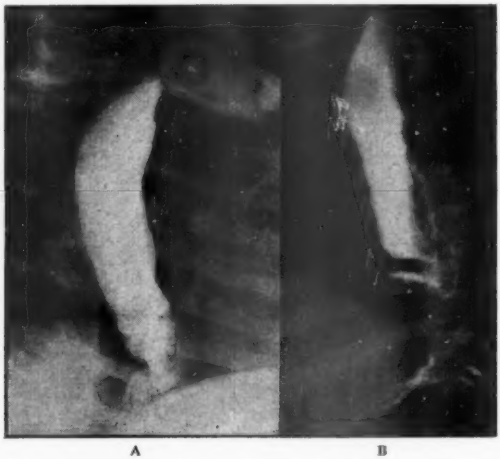


A B

FIG. 4 (*Case V*, pre-operative).—Foregut duplication cyst of the bronchogenic type, displacing the œsophagus and trachea.

the cyst and the child made what was clinically a quite uncomplicated and very satisfactory recovery. Radiologically, however, there was an extraordinary alteration in the œsophagus. A barium swallow

on the seventh post-operative day showed that it was dilated and tortuous, with several redundant curves in its lower third (Fig 5A, B).



A B

FIG. 5 (*Case V*, after removal of the cyst).—Post-operative cardiospasm.

It was alive with peristaltic activity, squirming about and varying the position of its curves. Nevertheless, barium was slow to pass down and remained in the œsophagus despite the intense activity. The examination was repeated two days later, with similar findings. On this occasion it was found that despite the stasis above the diaphragm, reflux from stomach to œsophagus was readily elicited. Another ten days later the appearances were much more normal. The œsophagus was less dilated and tortuous, with no abnormal peristalsis. A further week later, that is to say twenty-six days post-operatively, the œsophagus was slightly widened at the site of the removal of the cyst but in all other respects it behaved normally. There was neither retention nor reflux. During all the time of the fluoroscopic abnormalities the child was well and asymptomatic and she has remained quite well for the subsequent fifteen months.

DISCUSSION

In this last baby, the X-ray findings were something approaching those of the early stages of cardiospasm or achalasia of the cardia, as found in the adult. At operation the fibres of the right vagus nerve were seen to be spread over the surface of the mediastinal cyst and some fibres were undoubtedly disturbed or damaged during its removal. The left vagus was not seen but it also could have been damaged. In dogs, bilateral vagotomy at the level of the hila produces dilatation of the œsophagus and retention of its contents, as shown by Jefferson *et al.* (1951). The intense, inco-ordinated peristalsis and the easily obtained reflux are not easily explained on this basis, although either cardiospasm *or* excessive eructation may be a complication of human vagotomy for peptic ulceration. Stimulation of the vagus causes tetanic contraction of the œsophagus and relaxes the cardia, according to Samson Wright (1940). It seems, therefore, that in this child there were the results of both vagal interruption and vagal stimulation: dilatation and lengthening on the one hand and active but ineffective or inco-ordinated peristalsis and a relaxed cardia on the other hand. This dual effect could conceivably be a result of the partial damage to the vagi.

Such post-operative cardiospasm is obviously only an interesting curiosity. Does the usual type of cardiospasm, as seen in the adult, also occur in infancy? If it does, it seems that it must be exceptionally rare. In the adult, psychogenic trauma is usually considered the most important ætiological factor. Wooler (1952) said that the youngest case he had seen was a baby girl who commenced to vomit at 9 months old. He described her as a "highly strung only child. Apart from this infant his youngest subject was aged 2 years and 9 months. In addition to such cases which may be identical with the adult type there are a number of instances described in the literature at younger ages. Paterson, for instance, in 1942 described as an example of cardiospasm a baby first seen at the age of 18 days. The history was one of vomiting and failure to gain weight. Black material had been vomited and the stools were tarry. At 6 weeks old a barium swallow showed a dilated œsophagus with much narrowing and apparent spasm at its lower end. A mercury tube was passed daily, with disappearance of symptoms.

Other cases from the literature were reviewed by Thomson (1950). In all 13 babies, vomiting was the presenting feature. It began at the first to fourth day of life and varied from regurgitant to projectile in type. The prognosis was good. Thomson added 2 cases of his own that he considered examples of neonatal achalasia and in both there had been vomiting of brown material that was probably blood. In one instance the passage of a catheter relieved the obstruction in the lower portion of the gullet in a manner similar to that described in Case I. In the other baby it was noticed that the gap between the lower end of the œsophageal dilatation and the stomach was relatively rather more than one expects in cardiospasm as seen in the adult. Thomson entitled his article "Neuromuscular Inco-ordination at the Cardia in the Newborn". It is interesting to note that under this heading, presumably because of the clinical similarity, he included with his two cases of alleged achalasia a third baby that he considered to have an abnormality of a different type, namely cardio-œsophageal relaxation as described by Neuhauser and Berenberg (1947).

In recent years there has been appreciation of the importance in infancy of gastro-œsophageal incompetence associated with a small loculus of stomach above the diaphragm. Characteristic clinical and radiological features have been described (Carré *et al.*, 1952; Astley and Carré, 1954). Reviewing Paterson's and Thomson's cases, with their stories of blood-stained vomiting from soon after birth and with their illustrating radiographs, it seems highly probably that they were really examples of this condition, presenting radiologically as temporary obstructions in the manner I have just described. The same may well apply to other instances in the literature and it is suggested that so-called cardiospasm or achalasia in early infancy is usually spastic obstruction at an intrathoracic cardia.

Summary

(1) In infancy, temporary œsophageal obstruction just above the diaphragm, either complete or partial, usually proves to be associated with gastro-œsophageal incompetence and a small loculus of thoracic stomach. A single instance of apparently idiopathic spastic obstruction has also been observed.

(2) It is suggested that so-called cardiospasm in early infancy, with the exception of the post-operative type, is usually a temporary obstruction at an intrathoracic gastro-œsophageal junction and is not identical with the adult condition.

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Unusual X-ray Appearances in Hodgkin's Disease

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Hodgkin's disease, although the commonest tumour of lymphoid tissue, is a comparatively rare disease, only 300 cases having been seen in a large radiotherapy clinic like Westminster Hospital during the last fifteen years.

The cervical and intrathoracic lymph nodes and the spleen are the tissues most frequently involved, but practically any part of the body may be affected.

A sufficiently large series has not been collected to assess the incidence of unusual forms accurately. Most reports deal with less than 200 cases and in these the incidence of pulmonary lesions varies between 11% and 60%, and of bone lesions from 15–50%. There are only about 110 cases of gastro-intestinal involvement in the literature.

This is an unsatisfactory situation because accurate assessment of the extent of the disease is vital to successful treatment. It certainly appears that more elaborate X-ray investigations should be carried out, even if cervical glandular enlargement is the only clinical manifestation.

The classical X-ray picture of mediastinal lymphadenopathy may be due to many diseases. Although there are no characteristic X-ray appearances, Hodgkin's disease tends to involve the paratracheal and bifurcation groups more often than the bronchial groups. Conversely sarcoidosis and tuberculosis in recently tuberculinized peoples involve mainly the bronchial groups. Moreover, sarcoidosis and tuberculosis are nearly always bilateral, while Hodgkin's disease in its early stage is often unilateral and produces a much larger tumour in many

instances. These large unilateral lesions may simulate a dermoid, a substernal thyroid, thymoma, lipoma or even a bronchogenic cyst.

Pulmonary involvement is usually in the form of an interstitial infiltration. In its early stages it merely produces a little increased striation and is often overlooked or mistaken for a radiation effect. When more extensive it resembles tuberculosis very closely but usually has a patchy distribution in odd situations. The absence of calcification should always arouse suspicion. In later stages there are areas of consolidation and collapse which are frequently complicated by cavitation. While the plain film may resemble tuberculosis or chronic suppuration, the tomographs show the cavitation to be irregular and craggy, quite unlike the cavitation of tuberculosis (Fig. 1). In the rare instances in which a Hodgkin's cavity is

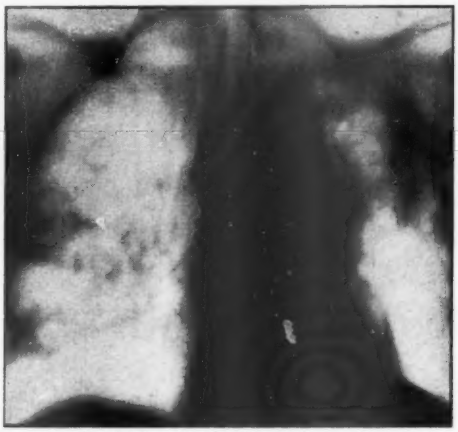

FIG. 1.—Tomograph showing irregular cavitation in the left upper lobe and several smooth cavities in the right lung.

smooth, the wall is unusually thick. In the Westminster Hospital series there have not been any tension cavities. In fact this type of lesion looks more like a late stage of an alveolar cell carcinoma or a fungoid infection than anything else.

It is estimated that in 1 to 5% of cases, tuberculosis occurs as a late complication of Hodgkin's disease. Superimposed tuberculosis cannot be diagnosed radiologically and it is of interest that these cases are resistant to chemotherapy. Rarely a Hodgkin's infiltration tends to be unilateral and around the hilum, so that it looks exactly like a carcinoma (Figs. 2 and 3).

Miliary Hodgkin's disease is very rare and indistinguishable from sarcoidosis. The foci are larger and less well defined than in miliary tuberculosis. Hodgkin's lymphangitis is also rare and identical with some forms of sarcoidosis. The presence of a large glandular component serves to distinguish Hodgkin's disease and sarcoidosis from lymphangitis carcinomatosa.

Round foci similar to metastases or tuberculomata are uncommon. They are sharply defined initially but as they invade they lose their definition and spread into the surrounding parenchyma.

Cardiac involvement is a very unusual late feature. The pericardium and myocardium are both affected. Obliteration of the normal cardiac contours as seen in constrictive pericarditis provides a clue to this complication. Invasion of the heart appears to be directly from the mediastinal glands.

SKELETAL CHANGES

Bone involvement is usually late although there are a few records where a lesion in a painful bone was the first manifestation. The bone lesions may be osteolytic (Fig. 4), osteoblastic or of the mixed type.

Although textbooks stress the solitary dense vertebra, this is the least common manifestation. Extensive osteolytic deposits are much more frequent but not often sought for. The spine, ribs, pelvis, proximal femora and sternum are most commonly affected. Exceptionally, lesions occur in the lower limbs and forearms. Single lesions are said to be due to invasion from adjacent lymph nodes, whereas multiple bone involvement is hæmatogenous.

The osteolytic and mixed types can simulate metastases from many malignant tumours while the osteoblastic type is similar to deposits from carcinoma of the prostate. Occasionally the appearances are similar to those of plasmocytoma (Fig. 5) or fibrous dysplasia. A periosteal reaction which is against fibrous dysplasia occasionally occurs in a long bone (Fig. 6).

FIG. 2.

FIG. 3.

FIG 4.

FIG 5.

FIG. 6.

FIGS. 2 and 3.—Unilateral Hodgkin's disease resembling a bronchial neoplasm.

FIG. 4.—Osteolytic lesion in the dorsal spine with collapse of the vertebra.

FIG. 5.—Osteolytic lesions in the pelvis.

FIG. 6.—Expanding lesions with a periosteal reaction in the lower parts of the femora.

As an example of the difficulty in detecting these lesions at an early stage, a child with thoracic and abdominal Hodgkin's disease had pain in the right groin and the film of the abdomen shows only a little increased density of the right pubis (Fig. 7).

FIG. 7.—Sclerotic lesion of the right pubis.

FIG. 8.—Involvement of the lower third of the œsophagus.

It has been suggested that the sclerotic bone lesions are not due to Hodgkin's infiltration but to a myelofibrosis following nitrogen mustard treatment. This is unlikely since the manifestations have been recorded long before nitrogen mustard therapy was instituted.

GASTRO-INTESTINAL TRACT

So far as the gastro-intestinal tract lesions are concerned these are usually gross and late and often cannot be differentiated radiologically from carcinoma (Fig. 8). Sometimes mesenteric involvement produces the steatorrhœic pattern in the small bowel and involvement of the wall of the small gut simulates Crohn's disease.

It would appear from the Westminster series that what are regarded as unusual manifestations of Hodgkin's disease are really comparatively common and should be searched for in every case.

I am indebted to Sir Stanford Cade, Doctor F. M. Allchin and Doctor P. Kerley for permission to describe their cases.

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JOINT MEETING No. 7

Section of Radiology with Section of General Practice

Chairman—J. F. BROMLEY, O.B.E., F.R.C.P.
(President of the Section of Radiology)

[*March* 18, 1955]

DISCUSSION ON RADIOTHERAPY IN MEDICINE AND SURGERY FROM THE GENERAL PRACTITIONER'S POINT OF VIEW

Dr. David Brown: In discussing the clinical use of radiotherapy in general practice it is best to consider it in two groups (*a*) cases of non-malignant disease and (*b*) cases of malignant disease. In doing so I shall not, of course, deal with the technical side, such as dosage, tangential fields, &c., but with its therapeutic value to us as general practitioners.

(*a*) *The Non-malignant Group*

Radiotherapy has proved of inestimable value in various dermatological conditions.

Firstly there are those skin diseases in which anti-pruritic action of X-rays is the main feature, for most itching dermatoses are temporarily relieved thereby. This property of X-rays, though maybe not of itself curative, puts the patient in the best position to overcome his ailment because it allays the symptom, which, in consequence of the human urge to scratch, accentuates the condition, or indeed, superimposes another on that already existing. Sleep is promoted, exhaustion relieved and the psychological attitude now regarded as so important is tranquillized. Amongst the cases so benefited are: (1) Neurodermatoses, (2) Eczema—especially dermatitis venenata, (3) Lichen planus, (4) Functional pruritis ani and pruritis vulvæ. In these latter cases it is important to find the cause, but in how many do we find that the cause eludes us? In many cases the relief is, of course, temporary and other measures must be pursued to promote recovery.

Next the group of cases in which the bactericidal action is brought into play. In this group it appeared at one time that the use of X-rays would no longer be necessary because of the discovery of antibiotics, but the fear of producing resistant strains of bacteria makes one wonder whether it would not be better to restrict the use of antibiotics to cases which do not respond adequately to X-rays. In this group I would place (1) Sycosis barbæ, (2) Recurrent furunculosis and carbuncles (though in the case of the single large carbuncle I would not hesitate to use large doses of antibiotic and X-rays), and (3) Plantar warts—a minor condition of the greatest nuisance value.

The anti-neoplastic action of irradiation is utilized to soften keloids, to bring about smooth and supple scars. It is noticeable how very rarely one sees to-day the hideous and disfiguring scars that were common thirty years ago. The action of X-rays in causing the shrinkage of nævi is of great value in the sensitive cases, and the cosmetic results have saved many from disfigurement and misery.

Then, in those cases where the action is in decreasing secretion, good results can also be obtained in seborrhœa, acne vulgaris (a condition particularly mortifying to the young of both sexes), and in hyperidrosis, although in my experience the results in hyperidrosis are not so beneficial as in the others. Lastly by temporary epilation in infections involving the hair follicles, e.g. tinea capitis, a hairy surface is temporarily changed to a non-hairy one and the site is made much more accessible to the other treatment.

Another large group of non-malignant cases met with in general practice, and in which radiotherapy is particularly helpful, are some gynæcological conditions. The fact that ovarian sterilization by this means is a comparatively simple method of treatment, and gives rise to little discomfort during treatment and few undesirable after-effects has enabled us to treat, by this means, such conditions as metropathia haemorrhagica, functional hæmorrhage, fibroids and endometriosis. It is most successful in those difficult cases of repeated floodings at the menopause which can be the source of so much ill-health in women and for whom surgery was formerly the only answer. In those cases of fibroids which

one does not care to allow to go on to natural menopausal regression, radiotherapy is of assistance in preventing much debility particularly when the fibroid is not larger than a 12-week pregnancy and is only an associated feature of the case. Although I have formerly recommended the use of X-ray in small condylomata of the vulva, since the introduction of podophyllin I have found the use of the latter very satisfactory in the few recent cases I have seen.

Other non-malignant cases met with in practice, which benefit from radiotherapy are: osteoarthritis and ankylosing spondylitis. The results in osteoarthritis of the spine occurring in patients usually of late middle age are particularly gratifying, for some amelioration is given, and my experience—albeit limited—is that pain is reduced, some mobility restored and the inexorable progress of the condition slowed. Ankylosing spondylitis is sometimes dramatically relieved, and as many cases are in young people the improvement results in their earning capacity being maintained, whereas without this form of treatment they would become a burden on the community; it is unfortunate that in young females one cannot apply radiation in the lumbar and sacral region without inducing at least temporary sterilization and most young women will refuse treatment and they cannot be blamed.

Those, then, are the common non-malignant cases, and I turn now to the second group, viz. of malignant cases met with in general practice and in which radiotherapy is employed.

(b) The Malignant Group.

Perhaps it is not surprising that we see more cases of malignant disease of the skin than of any other organ of the body, for the skin is the largest organ and, especially in these days of great industrial activity, the skin is very liable to be brought into contact with carcinogenic factors in certain oils and some other raw materials. In these cases of basal cell and squamous cell carcinoma of the skin and in cases of cancer of lip, we see in practice the triumphs of radiotherapy. There is no doctor of my acquaintance who would now prefer surgery to radiotherapy in these cases, in spite of the claim of some surgeons. And to those of us who used to see the veritable horrors of the end results of similar cases pushed away in small wards of the old workhouse hospitals, it gives a feeling of gratification that such sights have gone for ever.

In malignant growths of the tongue and buccal cavity, especially those situated in the accessible sites, and since the introduction of plastic moulds, the results are definitely improving. But much depends on the stage at which treatment is undertaken. My own experience is that lip and tongue malignancies are declining—as most cases were in men this may perhaps be associated with the decline in pipe smoking, particularly the clay pipe.

Nasopharyngeal and laryngeal cases treated by radiotherapy have not, unhappily, shown such success although in the former particularly one has been grateful for the relief of distressing symptoms afforded by this means, and I have always gained the impression that the patient's days have been lengthened as well as eased.

Carcinoma of the breast is second only to the skin in number, but causes us much more anxiety as so much depends upon when the patient presents herself as to the ultimate result. I would not presume to enter into the controversial issues of radiotherapy versus surgery in this condition, but as one on the touchline I feel that the common-sense view is: Stage 1, Surgery; Stage 2, Surgery and Radiotherapy, with a preference for Pre-operative Radiotherapy; Stage 3, Radiotherapy, sometimes with Surgery later; and Stage IV, Radiotherapy.

My next group of cases, which in number nearly equals that of breast cancer is that of carcinoma of the uterine cervix—a disease dreaded by the practitioner, not only because of the difficulties of diagnosis and the low percentage of survival rate, but because of the age distribution (70% being under the age of 55), mothers are removed from family life at a time when their influence and presence are most necessary. I can remember the late Mr. Bonney doing Wertheim's operation and claiming 60% survival after five years, but with other surgeons not getting such favourable results there was a swing towards radiotherapy. Recently there appears to be a recourse again to radical surgery as the method of choice. Be that as it may, it is a form of malignant disease which every practitioner fears, for the chances of survival, particularly if the case is at all advanced, are not high. In the case of the body of the uterus the results of panhysterectomy combined with irradiation seem to be somewhat better. Of the other parts of the female genital tract the ovarian malignancies seem to offer a better chance of a good result than the vulva which seems to resist both radiotherapy and surgery.

In the male the advent of the use of hormones has given us, I think, a method of prolongation of survival in carcinoma of the prostate equal to that of radiation therapy and has the advantage that the case is under the control of the practitioner from first to last.

It would, of course, be outside the province of a short paper such as this to enumerate all the malignant tumours met with in the body and which the practitioner seldom or never

seen, but I must mention the two sites where we have found that radiotherapy has been of little or no value to us—carcinoma of the stomach and carcinoma of the lung. Both these forms of malignant disease, especially that of the lung, are increasing—both depend for the slender chance of survival on early recognition and both tend to be most difficult to diagnose in their beginnings, because their early symptoms correspond with the symptoms of common and non-malignant conditions. Both are in the main insensitive to irradiation but the reports of the survival of a small number of lung cases does make one wonder if improvement in technique might yet bring about some improved results. Of the remaining malignancies which are seen in practice, there are two which come to mind—Hodgkin's disease and leukæmia. The former has always interested me as the first case I saw in practice was of this disease and I felt how shocking it was that our science could do so little either for cure or palliation. With the use of radiotherapy there is no doubt that the picture has changed and with full liaison between the radiotherapist and the G.P., cases, although the end is inevitable, survive for much longer periods and of the last two patients who died in my practice one had lived for nine years and the other twelve. It can also be said that radiotherapy, by reducing the gland masses and combating the secondary toxic manifestations, makes life bearable for those doomed patients. In chronic leukæmia, too, life is prolonged beyond what was formerly regarded as the prognostic term and unendurable symptoms are relieved.

Palliative treatment.—So often one has regretfully to reach the conclusion that neither surgery nor radiotherapy can be curative. The decision must then be taken whether the effects of radiation may be usefully employed in easing the patient—in many cases radiation expertly applied may greatly relieve the torture of malignant pain and delay the time when the drugs from which there is no retreat have to be given or when nerve section or blockage has to be done. Its value, too, can be very great when ulceration or profuse and offensive discharge is present, and the improvement by palliative therapy met with in these cases will frequently enable the patient to be nursed in his own home.

Conclusion.—Radiotherapy, like surgery, is not the solution to the problem of malignant disease—that solution lies in the womb of time—but it has been proved, and we see it in our surgeries and in our daily rounds, that in radiotherapy we have a therapeutic weapon that, in the right hands, is saving the lives of thousands of people who otherwise would have been condemned to die a lingering and miserable death.

Co-ordination between the radiotherapist and the general practitioner.—What we are both trying to do is to use this method of treatment to the greatest advantage to our patients, but too often this is not achieved because we work so much in isolation that much of what is accomplished in one field is little known in another.

In the actual treatment of the case the greatest aid that the general practitioner can give to the radiotherapist is in early diagnosis. The wide disparity in the results of radiotherapy between cases which are termed "early" and those which are termed "late" makes it imperative that those to whom the patient first has recourse should realize how great is their responsibility. I regret to say it, and I fear my old teachers would turn in their graves, but our own senses are not enough; neither are the stethoscope nor bimanual examinations; in fact, I am firmly of the opinion that any practitioner who waits for the diagnostic signs elicited thereby is a criminal. One, of course, must use one's clinical acumen and this does increase with experience, but we must all avail ourselves always of the scientific measures we now have at our command. As soon as the symptomatology of a case suggests malignancy as a differential diagnosis investigation must be pursued to the limit until proof has been obtained that it is not so. Although this may sound wasteful and consuming of medical man-power it is my strong feeling that it is the right of every patient of the cancer age to have all our resources at his disposal. By a careful assessment of symptomatology, by the greater use of diagnostic X-ray (and I am aware of the already great strain on this diagnostic aid) and controlled biopsy we can, I am sure, place more of our patients in the hands of the radiotherapist at a stage when his work can be so much more effective.

When the patient has been referred and accepted for treatment by radiotherapy it must be the radiotherapist's bounden duty, even when the case has been referred by another specialist—surgeon, gynæcologist, dermatologist, &c.—always to keep the G.P. in the picture. The patient is his patient, after treatment is concluded it will be upon him that the burden of ensuring that the post-radiotherapeutic measures will be carried out and it will be for him to encourage those for whom a favourable result is possible and to succour those for whom there can be no successful outcome. It is he who is perhaps the only member of our profession still practising the Art of Medicine who can apply the principles of his art to aid the efforts of those whose work is almost purely scientific.

The practitioner therefore must be kept fully informed of the treatment given, particularly on the return home of the patient—nothing is more damaging to the prestige of, and

confidence in, both the practitioner and the Centre, than delay in sending out this information. The patient feels that there is a great lack of interest in his case and tends to become less co-operative, and I am quite unconvinced that this prompt sending of information is so terribly difficult to do: it is often that its importance is not adequately realized. In Liverpool, the letter giving details of treatment is accompanied by a small memorandum on the after-care of patients who have received therapy and this admirable document, dealing as it does with the care of the sites irradiated is a good example of that co-operation which is so desirable and results in so much benefit to the patient. *En passant*, it does not mention radiation sickness—perhaps the condition does not exist in hospital practice but as general practitioners we do still see it though not so frequently as we once did. It is a difficult condition to treat. I have at various times used gastric and general sedatives but cannot say with much success. Latterly I have used Largactil in 25 mg. doses, and the results on the small number of cases have been encouraging.

Any important change in therapy should also be notified to the practitioner as sometimes this change is made without the practitioner being made aware and his grasp of the case may be correspondingly weakened.

Co-operation can also be most useful when considering the question whether palliative treatment should be used when it is realized that curative therapy can be of no avail. In making a decision on this issue, and it is a most important decision to make, no one can be more helpful than the family doctor. He should always be consulted before such therapy is undertaken for, in these cases, it is truly the patient who is being treated rather than his disease, and no one knows the patient and his probable reactions better than his own practitioner.

Turning to the broader aspects of the furtherance of this liaison I should begin with the student—I feel that the student does not get the opportunity that he should of seeing what radiotherapy does and how it works. This is most noticeable when the work of radiotherapy is divorced from the General Hospital. I know how loaded is the curriculum of the student but in at least two medical schools of which I have knowledge, there are no set periods for the practical study of radiotherapy. The student spends many hours watching surgeons perform operations for malignant conditions but never sees similar conditions treated by the radiotherapist, and his opinion in later life is often biased by this early lack of experience.

Later, when he sometimes realizes his need for knowledge of the subject, his opportunities are again limited. I know that there are post-graduate courses, but in the main these are provided for the people who intend to make X-ray work their career in medicine. I know, too, that practitioners are made welcome at most centres and most radiotherapists are delighted to consult with their G.P. colleagues, but what I should like to see, and what could so easily be done, would be that one afternoon each week (or each month) could be set aside when the G.P. would have the right to attend at the Radiotherapy Centre for consultation and the discussion of his cases. I should like to see, too, Clinical Assistant posts established in this specialty, just as we have established them in other specialties, where the G.P. can be given a post of some responsibility and be an actual working member of the team.

Our association should not confine itself only to the clinical side of our work; it should extend also to the administrative—in the Management Committee of the Centre, in the Hospital Board of the Region and in the Cancer Co-ordinating Committee of the Area the services and counsel of the G.P. should be utilized. Working as he does in daily contact with his patients in their own social and domestic environments, he is usually the most knowledgeable regarding the patient's needs and difficulties. It is also most necessary at times, in hospital planning, to have the services of a non-specialist but medical member to hold the balance between the specialties, and a general practitioner well versed in the work of radiotherapy could mould the opinion of the committee on the relative values of perhaps twin operating theatres and a linear accelerator particularly in these days of financial stringency when we cannot have both.

Dr. W. M. Levitt said that in the case of plantar warts it was very important after radiotherapy to take after-care precautions, and especially to avoid the use of adhesive plasters, which prevented free dissipation of sweat and moisture and rendered the skin particularly vulnerable to radionecrosis. Another point to be remembered was that if plantar warts failed to respond to radiotherapy they should not be turned over to ultra-violet irradiation. He had seen a case in which that had been done, with consequent blistering and ulceration.

Dr. N. S. Finzi, said how much he appreciated the collaboration between the radiologist and the general practitioner. In malignant disease, for example, a much more satisfactory

attitude was now taken. In the old days the patients with malignant disease who were referred to radiologists were of the hopeless type. That had all been changed as the result of many years of effort.

Dr. **L. W. Batten** said he would like to touch on the co-ordination between general practitioner and radiotherapist. He thought the two should meet or be in close touch before treatment began. The patient would ask the practitioner what it was for, what would happen, what likely reactions. He would not ask these questions—at least he seldom did—of the specialist, radiotherapist or other. He would go to the specialist, whether in hospital or elsewhere, and hardly ask a question, though many were forming in his mind, but when he got back to his doctor he would ask all the things he might have asked the specialist, and the doctor might not know the answers. It was very important that he *should* know the answers, and be informed about what would or was likely to happen, and when it did happen he and the radiologist should be in close touch. A full doctor's report was not to be expected every time the patient visited the radiologist—of course not—but unless information was forthcoming on the clinical phenomena to be expected, there would be trouble. Far too often the co-ordination was not close enough.

He was a little uneasy about the radiotherapist being entirely responsible for the treatment. Certainly it was for him to say what dosage should be given and how many attendances, but outside such details he thought consultation with the general practitioner was essential. It was for the radiotherapist to obtain any other specialist opinion required. He personally would accept that and welcome it, and would not feel that he or anybody else was being short-circuited. But the general practitioner would expect to be informed. Although it was a generalization, he thought that far too often the specialist was unaware of the questions the patient was likely to ask the general practitioner when he got home.

Dr. A. Talbot Rogers said that he also welcomed this suggestion for collaboration between radiotherapists and general practitioners, but it was not always easy to obtain. Radiotherapy was relatively a small specialty; there were only a small number of radiotherapists and they practised in some isolation from general practitioners. They were located at only a few Centres, and it was not always easy for a general practitioner to bring the patient to the Centre. In his experience he had found the radiotherapists with whom he had worked wrote frequently and kept the general practitioner in the picture by correspondence. But that was no adequate substitute for meeting in consultation. The Liverpool region might be more fortunate in this respect than some others. Last year, while on the Isle of Man, he had the pleasure of meeting Dr. J. S. Fulton, who was on the island conducting one of his regular follow-up clinics and who was obviously well known to the practitioners there. He did not know whether other members of the specialty travelled out to clinics of this type in their regions. Isolation in a fastness was not the best vantage point for promoting the liaison that was being advocated. It might be possible to have more peripheral consultative clinics, and if these were developed consultation could more easily take place between the radiotherapist and the practitioners of the area.

Dr. W. M. Levitt, who was asked to give his opinion on whether the patient should be told whether he had cancer, expressed the view that if he really wanted to know he should be told. He thought that practitioners acquired a keen sense of what it was right to do in these circumstances. If a patient said, "I have not got cancer, have I?" he usually did not want to know. But if he said, "I am a man of affairs and I have a family, and I want to know the truth because I want to settle up my affairs", then the practitioner would be under a legal duty to tell the patient the truth. Many patients who did not want to be told really knew, deep down, what the position was, but did not wish to face it. He had known experienced doctors who could not have failed to diagnose a cancer in another patient, persist in talking of their condition as if it were a benign one, even while undergoing a course of deep therapy. Such patients should not have a diagnosis of cancer forced upon them.

Dr. J. R. Nuttall desired to underline the advantage of the general practitioner accompanying the patient when possible. It was really a very great help, especially in the feeling it gave of increased security in the whole management of the case.

Dr. Brown had mentioned medical teaching. Most radiotherapy departments were attached to teaching hospitals and it was important that the radiotherapist should contribute to undergraduate education. Although no good purpose was served by teaching radio-

therapeutic technique as such, students should be so instructed that when qualified they could answer necessary questions put by the patient or the relative.

The concentrated clinical material of the radiotherapy department should also be used to teach the student to recognize cancer and to suspect it when he met some of its less usual presentations.

Mr. Anthony Green said that he had been glad to hear X-ray therapy recommended for plantar warts in children. One of the important things in this connexion was the favourable psychological effect on the child compared with the other methods used which were either painful, uncomfortable or time-consuming. With regard to the possibility of radiation injuries which have been reported in the past he had consulted with plastic surgeons to find out the lowest dose which ever produced any injury. After a number of trials he found a method whereby a single safe dose was given with a very high degree of success. He expected to publish in the near future the details of this method of single dose whereby long-term follow-up of a considerable series of cases proved that there were no undesirable effects whatever. He hoped that this would establish the safety of the method beyond any reasonable doubt and so commend it to widespread use.

On the question of telling a nervous patient the diagnosis when he was suffering from cancer: for the patient who could not "take it" he was in the habit of reading out the pathological diagnosis. The patient being told he had a squamous epithelioma seemed to be satisfied and had little idea what it was.

Mr. Jackson Richmond also stressed the importance of early diagnosis of carcinoma. However, he regretted to say that patients were seen all too often who had sought medical advice a considerable time before being ultimately referred for treatment. This applied particularly to cases of breast carcinoma, and probably had its origin in undergraduate teaching. A very good maxim was "a lump in the breast should be regarded as malignant until proved otherwise".

One other point concerned untoward constitutional side-effects following irradiation treatment. It seemed probable that there would be a great increase in the volume of literature dealing with this subject in the near future, particularly because of the increasing studies on nuclear fission. He made a plea for the interpretation of published results to be made in proper perspective with due consideration of all the factors occurring. It would be a very great pity if radiotherapy came into even partial disuse because of the fear of precipitating dangerous constitutional effects.

Dr. David Brown, in reply, said on the question of the artificial menopause that he could not see any objection to the radiotherapeutic method given in the appropriate case and under carefully controlled conditions. Here they had a woman, usually of about 40 or 45 years of age, busy in her family, who, if the radiotherapeutic treatment were given, was taken away only for a day, whereas the surgeon might take her away for three weeks, thereby causing a complete upheaval in her home.

The next thing was the psychological approach to the patient when a condition had been diagnosed as malignant. There again, he thought, the general practitioner was the most important figure. It was he who knew best whether to tell the patient or not because he had already seen that patient at some crisis of his life, and knew what was the extent of his fortitude and courage and whether he was the type who could not take what the public still thought of as a sentence of death. He was not sure that it was always the man of affairs, of whom Dr. Levitt had spoken, who should be told: it depended on his individual make-up.

In this connexion the effect of names was not unimportant. They had changed the name of the old "Cancer Hospital" to "Radium Institute" and "Radiotherapy Centre", and that had worked well for a time, but to-day many of the patients were not quite as stupid as they thought them and they knew what these new titles signified or might signify. Radiotherapy centres should publicise their non-malignancy work very much more than they did, so that the patient did not think of them as necessarily connotating the treatment of malignant conditions.

Anyone who worked on Cancer Co-ordinating Committees knew that the education of the public was one of the big problems confronting them. The fear of malignancy was so great that it would be unwise to tell the public too much about cancer. A great deal depended on how it was told, and the person who could do these things best was the general practitioner. He could educate the patient in this matter, and also in the beneficial effect of radiotherapy and surgery in early malignancy.

The last thing concerned medical students. Radiotherapy should have its due place in the curriculum.

Section of Comparative Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bart., M.A., D.M., F.R.C.P.

[*May* 25, 1955]

SYMPOSIUM ON FACTORS INFLUENCING HOST-PARASITIC RELATIONSHIPS

Dr. E. L. Taylor (Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food, Weybridge):

An Ecological View of the Non-specific Factors Controlling Parasitic Disease

The stimulation of the imaginative faculty is one of our earliest pleasures and, I am happy to think, is one that most of us are able to retain throughout our working lives. Our President's opening address (*Proc. R. Soc. Med.*, 1955, **48**, 13) has done much more than please us, however; through asking difficult questions and suggesting answers of an altogether unexpected kind he has succeeded in making us use our imaginations constructively. In reading again through his Address one is tempted to suppose that there must be some underlying principle concerning susceptibility to disease, something apart from the details of antigens and antibodies that will explain a whole host of mysteries; such a big idea, for instance, as that of Steenstrup on the alternation of generations in invertebrate animals; or the demonstration of the truth of the microbial origin of infectious disease—Where, then, shall we look for this key?

Adjustment of host and parasite.—It has often appeared to me that in the matter of host-parasite relationships there are advantages to be derived from working with metazoan parasites in that certain things become obvious merely because of the size of the parasites. The concept of these organisms carries with it an idea of individuality that is denied the rabble of a bacterial colony. If one is dealing with metazoan parasites one is able to see when a parasite is sick or when it is not properly looked after by its host, or that the two partners, host and parasite, are not getting along together, as they ought to do, and as they had agreed to do in their co-evolution. We know, for instance, that the rate of egg production in female nematodes is depressed as a result of resistance developing in the host, and that host nutrition affects the size and rate of growth of at least some of the nematode and cestode parasites; we can see it happening to individual parasites.

One of the more obvious points is the "essentially" harmless nature of the majority of these parasites, which may often be present in considerable numbers without giving rise to obvious disease. This harmlessness is presented in the ecological view that I am putting here, as a sort of ultimate goal of perfection in parasitism, towards which all parasites tend to evolve.

A further point made obvious to the worker with metazoan parasites concerns the duality of the mechanism of immunity relationship. Whereas the bacterial immunologist has been able to show a number of changes that the parasite brings about in the blood of the host, and understands much of specific host-resistance, he possibly tends to disregard the parasite itself and may not give enough attention to the useful idea that it takes two species to make a condition of parasitism.

The worker with metazoan parasites on the other hand more readily thinks in a sympathetic way of the parasite's point of view. He is tempted to let his imagination run (perhaps too fast) along the lines of immunity mechanisms in the parasite comparing in complexity with those of the host. He might presume, for instance, that it would be possible to vaccinate a susceptible young parasite against its host, or, but for the difficulties of technique, to prepare a hyperimmune parasite serum that would save the life of many a parasite. These ideas may doubtless be regarded as having no application to micro-organisms—but perhaps we should not be too certain of that point. If the perfect parasites have "learned" these reactions is it not likely that those less perfectly adapted are, at least, on the way? The meaning of the word "immunity" still continues to broaden and the more fitting term

"host-parasite relationship" to take its place as the parasite makes an increasing claim for consideration. This broader term presents the position in the ecological way of relationship to environment and of the continuity of the integrated ecological unit as a whole, host and parasite together. The question that we are to answer is not so much "does an individual parasite harm an individual host?" as "can one parasite species live with a host species?" It is the life of the species that we have to consider, and if we let our imaginations run along those lines we might even suppose that the immune responses of the host species to many species of metazoan parasites are markedly in favour of the survival of the parasite species, since the absence of resistance would result in too plentiful a reproduction of parasites and ultimately bring about the extermination of the host and the parasite species as well.

Multiplicity of factors involved.—So much for the perfection of parasitism and of the need for a parasite to adjust to its environment. I should now like to consider more specifically the matter of ecological adjustments, and to present a view of the co-evolution of all of the creatures that comprise an ecological unit. It would seem that in each unit there has been a constant trend for organisms to make use of whatever there may be in their environment, so that they grow into the environment and evolve to fit it with perfection and to make use in their economy of everything that is normally present.

One or two examples of the integration of an ecological unit might be valuable at this point. That of bush sickness of sheep and cattle in Australia is a good one, the investigation of which ultimately revealed a deficiency of cobalt which was required, not directly by the host, but by the bacterial flora of the rumen, for the building up of the vitamin B_{12} that was essential to the health of the ruminant host.

This example is a particularly suitable one because the salient features can easily be discerned and clearly separated from one another. The sheep evolved to fit a certain ecological environment that must include the presence of specific bacterial organisms, and of cobalt, in order that it may be supplied with a vitamin that it cannot manufacture for itself and cannot find in any other way.

Further examples of this same kind are now coming along subsequent to the employment of prolonged administration of sulphonamides and antibiotics, quite a number of vitamin deficiencies having now been recognized in farm animals that have been maintained for a prolonged period on rations medicated in this way. It would now seem, therefore, that the animal is dependent not only on all the nutriments that have been so long recognized, but on the presence of certain organisms, perhaps of many different kinds, the balance of whose populations is maintained by forces not yet understood and the products of whose metabolism have become an essential to the existence of the host. Still further insight into the complexity of these interrelations is given by the pathogenicity that is sometimes assumed by ordinarily harmless micro-organisms during the protracted administration of antibiotics. This observation opens yet another window into the complexity of the balance, and the perfection of the tension that controls the relationships of the many organisms in an ecological unit.

As a second example of complex relationship let us consider the factors that control the numbers in the communities of strongyloid nematodes in grazing horses. This ecological unit consists of suitable soils, of moisture and temperature suited to the growth of certain herbage plants, and of horses to graze there so that, from the worm's eye view, the nematodes may live in their bowels. In the ordinary way the nematodes live for a long time, probably for years; a mechanism is necessary, however, for the restriction of the population, otherwise their immediate environment, which is the gut of the horse, may be so changed as to be completely destroyed, and all will perish.

There can be little doubt that the primitive ancestors of these worms were laying down the foundations for this balance long before the advent of *Eohippus*, the most primitive ancestor of the horse that palæontology has recognized. If we begin to search for the mechanism the first ideas to which we naturally turn are those connected with what we have been able to observe of the immunity mechanisms that endeavour to overcome bacterial invasion; but those, I submit, should be considered as only a small part of the enormously complex array of forces that have been integrated in that ecological unit towards the adjustment of nematode population. There are also certain very complex responses on the part of the parasites. Gibson's work at Weybridge, on one genus of these worms, has shown, for instance, that the mucous membrane of the colon of the horse is only receptive of infection in early life, and apparently only while, as a foal, it is receiving mare's milk. Furthermore that the majority of the larvæ then acquired remain in a dormant state in the mucous membrane, for months or perhaps years, only proceeding with their full development to make up the depleted population of the lumen. These adjustments seem sufficiently complicated but we must also recognize as part of the adjustment that has evolved, the specific responses that cause the horse to avoid the proximity of fæces while grazing and to defæcate

only in certain parts of a restricted grazing area. It is through all of these many factors that the component parts of the ecological unit are integrated into a whole which operates harmoniously, populations are balanced and the continuity of the nematode species is assured.

As a final example I shall refer to an observation of Professor Wetzel of the University of Giessen who in a private communication informed me of an interesting association that he had observed between the small nematode *Strongyloides westeri* and the horse. This worm very commonly occurs in foals, which develop a heavy infestation that is, however, soon thrown off. We had often observed at Weybridge that no matter how carefully the pregnant experimental mares and the foaling boxes had been washed and disinfected the foals could not be kept free from infection. Professor Wetzel described to me how during his experience of large numbers of serum-producing horses and mares he had observed the same thing, and how ultimately he had carried out daily examination of the fæces of the mares, up to the time of foaling and had observed that a few days before parturition, at about the commencement of activity in the mammary gland, the eggs of strongyloides appeared in the fæces. He felt there to be little doubt that the oviposition of female worms that were, presumably, lying dormant in the mare, was activated by the hormones that appeared in the circulation of the mare at that time. It is by this highly complex means that the nematode species has adapted itself to continue life with the equine host.

I should like to present these examples to you as small windows through which we may gain a little insight into the complexities of host-parasite adaptations and in support of the idea that—in so far as the old parasites are concerned—disease is the outcome of an interference with the ecological balance. It follows, therefore, that because the evolving organisms have acquired a dependence upon so many and such varied substances concerned in one another's metabolism, the non-specific factors associated with parasitic disease will be of an equally diverse nature.

Delicate nature of the balance.—Not only are these relationships extremely complex but the delicacy of the balance is often exceedingly fine. A good example is provided by certain observations made during the intensified work on schistosomiasis carried out since the war. This work has revealed that although no difference either morphological or biological can be detected between certain host snails from different regions of the world, or in the schistosomes themselves from those two regions, neither as they occur in the intermediate host, nor in the final host, yet the schistosomes from one region are unable to develop in the snails from the other.

This incompatibility presumably has nothing to do with the ordinary phenomena of immunity, but is rather to be regarded as of a physiological nature. In using that word, I am perhaps only trying to hide abysmal ignorance, as I cannot say what these physiological factors might be that have adapted these two organisms so delicately to one another. There is, however, a great deal of evidence of the widespread occurrence of these slight variations developing even within the last few thousands or tens of thousands of years, as is witnessed by the susceptibilities of the aboriginal inhabitants of South America or of Polynesia to measles and tuberculosis, or of Europeans to malaria in foreign parts of the earth.

This moving of populations, or of parasites, about the face of the earth is, indeed, one of the main causes of epidemic disease, which is an outcome of the maladaptation of host and parasite, so that a long list could be compiled of diseases caused by parasites that, by some chance, often as a result of man's interference, get into the wrong host. Among these may be mentioned the relative harmlessness of trypanosomiasis among the indigenous African animals; the benign nature of histomoniasis in the chicken; of American swine fever to the American peccaries, or of African swine fever to the wart hog. To those need only be added the example of myxomatosis in South American and in European species of rabbit where the virus is so ill-adapted as to be threatened with extinction along with its host.

It would appear, therefore, that in many instances the borderline between successful parasitism and disease is an exceedingly narrow one and it may be supposed that the changes required to upset the balance are not only of a very varied nature but sometimes need only be very slight in order to allow an ill-adapted parasite to multiply exceedingly and to cause disease. Most of these variables hinge on the physiology of the two organisms, and in the examples quoted are doubtless to be regarded as dependent upon essential attributes of the species of hosts concerned. It seems not unreasonable to suppose, however, that temporary changes also occur. Groups of animals are sometimes found, for example, to be highly susceptible to the toxic action of drugs, as in sheep to carbon tetrachloride, apparently associated with diet. May we not suppose, therefore, that small variations occur from time to time, in the animal body perhaps in tensions of salts, or in availability of certain substances to invading parasites, such as vitamins or hormones, that occur only in minute quantities. As an example, there is a certain rhythm that we have observed in the

egg production of nematodes in the sheep and that we were unable to explain except as an effect of circulating hormones. Professor Wetzel's observations on strongyloides reflect the same mechanism. Is it not possible that the increased susceptibility of man to tuberculosis at the age of 15 may be explained in the same way?

Competition among cells.—And this brings me to a final consideration of the factor of competition between living organisms. In the ecology of free-living organisms, whether plant or animal, the reproductive potential is always more than adequate, so that each species fills its ecological niche to a maximum that is determined by competition from other organisms. If a vacancy is created by the elimination of any species, then the room so provided is quickly occupied by some other. We have seen how certain normally harmless microbial inhabitants of the animal body take on pathogenic characteristics if certain other organisms are suppressed through the prolonged administration of antibiotics, presumably because the competition that normally keeps these organisms in their place has temporarily been suspended. We are used to thinking of the effects of overcrowding as a simple outcome of competition for food; there may, however, be other factors, as the recent work of the microbial ecologists would seem to suggest. As I understand it, the impressive point to these workers in observing the succession of events in their elective cultures, is the exceedingly fine adjustment of the organism to its environment so that there would seem to be one specific microbial organism that exactly fits a given environment and enables it to dominate and crowd out the rest. There would seem to be more behind it than a mere matter of thriving a little better than the rest, something, perhaps, like the PABA-starvation of bacterial cells in the presence of sulphonamides. This we may regard as yet another peephole into complexities, those of the chemical mechanisms by which micro-organisms compete for food. It seems not altogether unreasonable to suppose that the factors in this competition between micro-organisms may also operate in the animal body as between the cells of the parasite and those of the host, so that in certain instances the parasite is able to multiply through securing food essentials that are usually monopolized by the host cells.

SUMMARY

This short paper endeavours to present an ecological view of the factors affecting relationships of hosts and parasites. Most of the examples have been taken from the helminths and there is plenty of room for argument on the differences between these metazoan parasites and the less well-adapted microbial parasites. If, however, we regard the helminths as the patriarchs of parasitism, well on the way to perfection, it helps in the understanding of the general trends and the goal towards which the less well-adapted parasites are moving.

If the ecological view has turned out to be a panorama and does not appear to focus on any particular point it is because I see it as a tremendous complexity of innumerable factors of great variety integrated in each example into a whole. In these communities a balance is maintained between reproduction potential on the one hand and the environmental limitations on the other. This balance is of an exceedingly delicate nature and is easily upset so that the parasite population may increase beyond its normal limits and disease result because the relationship has become unnatural.

Professor A. A. Miles (Lister Institute of Preventive Medicine, London):

The Experimental Study of Non-Specific Immunity [Abridged]

The study of non-specific immunity, particularly antibacterial immunity, has rather fallen into neglect; there is a good deal of haphazard descriptive information. We know, for example, of non-specific bactericidal substances in the blood fluids and in the leucocytes; of the bactericidal power of the blood and its modification in disease states; and that sometimes the injection of antigens induces some non-specific immunity to infections with antigenically unrelated organisms. More recently one aspect of these non-specific defences begins to be more precisely elucidated in the studies of Pillemer (1954) and others on properdin and related substances. Non-specific immunity nevertheless remains rather a Cinderella of experimental pathology. This is perhaps because of the enormous enhancement and acceleration of what are recognized as non-specific defences, when antibody is present; consequently non-specific reactions appear as rather feeble things awaiting the magic touch of antibody to transform them into something really effective. We need to know more of two things: the precise value of non-specific immunity in keeping us healthy and in combating established disease; and the factors which maintain non-specific immunity and whose destruction or inhibition in the natural state leads to the establishment of infection.

In our exploration of non-specific immunity, however, we are subject to a major technical restriction. In most infective diseases, specific antibody formation is either demonstrable, or may be reasonably expected to have taken place by the time the infected animal is beginning to overcome the parasite, and is on the way to cure; and although at this stage useful anti-microbial reactions that are independent of specific antibodies are likely to occur, it is very difficult to estimate their contribution to the resistance of the infected host. We can avoid this difficulty by confining the study to the early stages of infection; but we must bear in mind that the results will elucidate, not resistance to established infection, but the resistance to becoming infected at all; and factors relevant in this restricted context may be irrelevant in the context of established disease.

Resistance to infective disease may be virtually a total insusceptibility, like that of the hen to tetanus. The elucidation of species insusceptibility of this kind is rather remote from our problem; our immediate concern is relative insusceptibility within a host species; in other words, how an animal manages to remain uninfected, by microbes that are known on occasion to infect it, in the face of the numerous microbial hazards of its environment.

The answer should properly be sought in an experimental model that closely resembles the natural circumstances, as in Topley's work on mouse typhoid (*see* Greenwood *et al.*, 1936). This entails an elaborate and expensive set-up, and economics usually preclude us from imitating the hazards of natural infection. We must either inject the test microbe somewhere, or at any rate push it into the lung in measured aerosols, or into the gut in a measured feed. In doing this, we may be a long way removed from the natural infection; with injection, certain mechanical or functional barriers are by-passed; and with aerosols and infected feeds, we may be well outside the time and concentration conditions in which natural infection takes place. These points must be emphasized as a caution against interpreting results of such experiments too readily in terms of the natural invasion.

When the microbe is in the tissues, its fate may be studied locally or generally. General disease or death after infection is a perfectly good index of immunity, but in depending on it in the exploration of early events, we are assuming that when a given dose of microbes has been injected, the result is pre-determined, and we are at liberty to argue from the ultimate fate of the animal to any point in the long and complicated process of infection, from the primary lodgement onwards. This may be true, and the dose-response of animals to certain pathogens is consistent with this view (*see* e.g. Peto, 1953). There is, however, little evidence against the view that during the progress of infection, from primary lodgement onwards, there is a sequence of events, any one of which may decide the issue of survival or death.

Simple observation of the defensive processes does not take us beyond descriptive biology. If we are to analyse, we must interfere, and find the things which either improve or destroy the defences. It is unfortunate that, apart from directly antibacterial agents like antibiotics, we have as experimental tools so few procedures that improve non-specific immunity. For the most part we depend upon modifying or destroying resistance in one way or another, and hope by analysing the effect of these inhibitors of resistance to define the reactions upon which non-specific immunity depends. It is usual to try systemic modifications; such as the destruction of the lymphoid-macrophage system by X-irradiation, the destruction of certain defence cells by nitrogen mustards; poisoning by dicoumarol and ethyl alcohol; starvation by deprivation of certain dietary components, like the vitamins. What do we get out of these? I suggest that in making tests of this kind, we are much more using non-specific immunity as a tool for exploring the field, say, of radiation biology or nutrition, rather than that of non-specific immunity. Because, apart from showing that, e.g. the polymorphonuclear cells or the reticulo-endothelial system must be relatively intact if the animal is to resist invasion, we have not got very far. It does not take us very far to know that when an animal is severely damaged in one way or another, it loses resistance. The animal pursues its ordinary life in a healthy equilibrium that resists a large number of stresses; and we shall best understand non-specific immunity when we can elucidate the small defects in the maintenance of equilibrium which lead finally to the appearance of manifest disease. In other words, we must avoid not only experimental circumstances that are too remote in kind from the natural process, but also procedures that are too remote in degree. When we alter resistance by relatively brutal interference with the general health of the animal, we may fail to elucidate events like the establishment of an infective focus at the primary lodgement of the infecting bacteria, which may be determined by local, not systemic, factors.

We must avoid "getting out on a limb" of brutal experimental procedure, and then hoping to intrapolate from the brutality to the finely adjusted reactions that determine immunity. Menkin's hypothesis of lymphatic blockade (Menkin, 1940), formulated in the first place after a study of gross pyococcal and turpentine abscesses, is inapplicable to decisive events in the infected tissues at the time of the primary lodgement (Miles, 1953–54). Another example of working at extremes can be found in the habit of using highly virulent test

bacteria (perhaps because experimental infection with virulent organisms tends to be far more reproducible than infection with moderately virulent); but, except perhaps in the midst of a raging epidemic of a contagious disease, where are we likely to find among natural infective hazards, the parallel of an organism in its logarithmic growth phase, which is so virulent that introduction of one hundred or fewer cells inevitably kills? In nature, the animal is much more likely to be exposed to bacteria that have survived the prolonged hazards of the external environment and need a recuperative lag phase in the new host's tissues before reproducing their own virulent kind.

A field of investigation then that is likely to yield significant results in the study of non-specific immunity is that of local infections with moderately virulent organisms, using minimally effective amounts of modifying agents for the analysis.

The following examples illustrate the potentialities of this approach, using local injections in the guinea-pig skin. The skin is probably a less representative portal of entry than the more penetrable and softer epithelial surfaces of the respiratory, alimentary and genital tracts, but it is a useful tissue to begin with because the progress of local lesions can be more readily seen; and both injected microbes and locally injected modifiers stay longer in a tough tissue like skin than when locally applied in, say, the lung or the gut. Moreover, in the skin of a large animal, like the guinea-pig, a very large number of lesions, both treated and untreated, can be studied in a single animal, thus avoiding some of the difficulties of inter-animal variation within an experimental group, because the control infection is on the same animal as the test infection.

Effect of anticoagulants.—If anticoagulants prevent the formation of fibrin barriers, and therefore, according to the hypothesis of lymphatic blockade, promote the spread of infection, we might expect a local enhancing action. The anticoagulant sodium polyanetholsulphonate (liquoid) in fact greatly enhances skin infections by staphylococci, streptococci, corynebacteria and clostridia. But liquoid is also an anti-complementary substance, and when we use heparin in doses that are approximately five times as anticoagulant as liquoid, there is very little enhancement. This dose of heparin has, compared with liquoid, only 1/15th to 1/30th the power to inhibit phagocytosis, to inhibit complement, to inhibit the chemotactic activity of leucocytes, and to destroy the bactericidal action of the blood. A pure anticoagulant action, therefore, does not appear to affect the course of the local infection. Smaller doses of heparin, indeed, depress infectivity. For example, 0·5 i.u. of heparin in 0·1 ml. injection-volume substantially reduces the lesion-diameter infections with streptococci and with *Listeria monocytogenes.*

The local effect of malonate.—Berry and his colleagues (1954) showed that malonate in systemic doses of some 20 mg. greatly diminished the resistance of mice to *S. typhi-murium.* In similar concentrations locally (i.e. 0·2 to 1 mg./gram of skin), malonate depresses, not enhances, the infectivity of *L. monocytogenes,* a Group C streptococcus and *Corynebacterium ovis* though it slightly enhanced the activity of *E. coli, Ps. pyocyanea* and *P. vulgaris.* Nevertheless, although the infectivity of these first three organisms is depressed with a higher dose of malonate, when the dose is reduced to the region of 10 μg. in 0·1 ml., the infections were definitely enhanced. These results are preliminary, but are worth citing if only as an example of the amount of information that can be got from a study of local lesions; because all the above facts were elicited from some 30 guinea-pigs. The amount of information per animal, using as indicator the quantal response with lethal infections in mice, is far less.

Stimulation of non-specific immunity.—By similar methods, it is possible to make extensive studies of various infections, and by measuring the effect of local modifying agents to arrive at useful estimates of the numerical value and the duration of the local defence reactions (Miles, 1953–54). The method, of course, has pitfalls, but even these are instructive. For example, the several lesions present on one animal influence each other. Thus, when intradermal staphylococcal lesions are made in the belly of the experimental animal and streptococci titrated in the skin of the back, the ultimate size of the streptococcal lesion is large when the streptococci are injected at the same time as the staphylococci. But when the staphylococcal lesions have been established for as little as two hours before the streptococci are introduced, a substantial degree of non-specific immunity is evident from the diminished size of the streptococcal lesions initiated at this time. Skin titrations of this kind are a powerful tool for making a quantitative study of non-specific immunity stimulated in various ways.

The delicacy of the method is evident from some experiments made in the first place for the purposes of control. In many cases we wish to find what happens when bacteria are injected into skin sites that have been prepared with a previous intradermal injection of a modifying agent. As a control, the bacteria were injected into skin that had received only an intradermal injection of saline; but even here we found that, although bacteria injected

immediately into the saline were fully infective, they were much less infective when injected into the site of a four-hour-old saline lesion; yet neither physiologically nor histologically could any difference be discovered between normal skin and a four-hour-old saline lesion.

These are a few illustrations of the many aspects of this technique and its use for the study of non-specific immunity. I have put forward no general experimental thesis, but have tried in the main to discuss the strategy of research into non-specific immunity. Tactics are equally important, but I have touched on them only in so far as they concern the limitations of the many experimental techniques open to us for answering the fundamental questions that the phenomena of non-specific immunity put to us.

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Mr. F. C. Bawden (Rothamsted Experimental Station, Herts) dealt mainly with the various ways in which the altering of the conditions under which plants are grown, and so altering their physiology, alters their susceptibility to viruses. Mr. Bawden emphasized that these differences were not influenced by antibody formation, for there is no evidence that plants produce such things. Once systemically infected with a virus, a plant usually stays so as long as it lives. This striking contrast between virus diseases of plants and animals was no indication that the viruses affecting the two kinds of organisms differ, for plant viruses were excellent antigens when injected into animals.

Almost any change in the conditions of growing plants influenced the ease with which they became infected, the severity and type of symptoms they showed when infected, and the extent to which viruses accumulated in them. Usually the severity of symptoms reflected the virus content, but this was not always so when nutrition was changed. Infected plants deficient in nitrogen and phosphorus showed more severe symptoms than those fed adequately, though the well-fed ones contained much more total virus. Well-fed plants might contain as much as 10 grams of tobacco mosaic per kg. of fresh leaf, about one-quarter their total protein, and although starved plants contained less, it might amount to two-thirds of their total protein. This virus was a major component of infected plants, and could account for more than 10% of their dry weight.

Conditions that increased the ease with which healthy plants became infected were not always those that also increase the extent to which viruses multiply in infected plants. Indeed, the two were often strikingly different. Keeping healthy plants in the dark, or at temperatures around 36°C., for a few days before they were inoculated, greatly increased their susceptibility to infection, but the highest virus concentrations were achieved in infected plants kept in bright light and at temperatures around 20°C. There was evidence that some viruses both multiply and become inactivated in plant cells and that the concentration they reached reflects the balance between the two processes. High temperatures encouraged the systems responsible for inactivation, and plants could be cured from some virus diseases by being kept continuously at 36°C. for ten days or more.

It was often assumed that great virulence towards a host was evidence that the host had only recently been exposed to the parasite and that ability to tolerate infection reflected a long association between host and parasite. Work with plant viruses suggested this assumption was far from being universally true. When plants were exposed for the first time to a plant virus, they were equally likely to be affected severely, moderately, or to tolerate infection without showing any signs of disease.

Colonel H. J. Bensted (Central Public Health Laboratory, London):

In connexion with non-specific immunity reactions associated with infestation with metazoan parasites, Colonel Bensted drew attention to references in the literature (Hiles, 1926) to the presence in "normal" rabbit sera of natural complement-fixing antibody to the antigen derived from larval forms of *Echinococcus granulosus*. In a preliminary investigation

of this phenomenon he had not found that the presence of the complement-fixing antibody was associated with any obvious tænia infestation of the rabbit and although it was not universally present, and when present varied considerably in intensity, it did appear to be related to the identity of the host providing the hydatid antigen used in the test. When the reaction was observed it was much more intense with an ovine antigen than with a bovine antigen. With two such antigens standardized against a serum prepared by injecting washed *Echinococcus granulosus* scolices into guinea-pigs fixation might be insignificant with a bovine antigen yet be demonstrable in high titre with sheep hydatid antigen. At the same time such a rabbit serum would fix normal sheep-brain antigen to an even higher titre. Moreover fresh scolices of *E. granulosus*, which could successfully remove hydatid complement-fixing antibody from human sera from cases of true hydatid disease, failed completely to remove this reacting substance from rabbit sera. This strongly suggested that the reaction was non-specific.

Somewhat similar results, but much less marked, had been noted in an individual very recently immunized with anti-rabies vaccine in the form of a sheep-brain suspension. At present no satisfactory explanation could be offered and further experimental work was in progress.

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Dr. H. O. J. Collier said that Professor Miles' results with heparin illustrated the value of avoiding crude experiments, since, by using small doses, he was able to show that heparin enhances non-specific immunity, which was not apparent with larger doses. This demonstration was also interesting because heparin was known to be stored in the mast cells along with histamine and the two substances might be liberated together. This made Dr. Collier still wonder, in spite of Professor Miles' warning, whether histamine did not, perhaps along with heparin, play a natural part in non-specific immunity. Another interesting observation of Professor Miles was the enhancement of non-specific immunity by the prior injection of saline. Could Professor Miles tell them the time-course of this phenomenon: did it correspond with the histamine release that could occur in response to slight injury?

Professor A. A. Miles, in reply, said that the role of histamine in local infections was difficult to assess because the simultaneous injection of small doses of histamine and bacteria led in some cases to a slight enhancement of the local infection and in others to a slight depression, depending partly on the nature and partly on the dose of the bacterium. Histamine does not appear to mediate the local immunizing effect of intradermal saline, using local increase in capillary permeability as an indicator of its presence; because saline does not induce any increased capillary permeability, either on injection or at any period during the subsequent four hours.

JOINT MEETING No. 8

Section of Comparative Medicine with Section of Pathology

Chairman—Professor L. P. GARROD, M.D., F.R.C.P.
(President of the Section of Pathology)

[*March* 16, 1955]

DISCUSSION ON TOXOPLASMOSIS

Dr. **J. Chr. Siim** (Copenhagen, Denmark)[1]:

Ætiological Investigations in Acquired Toxoplasmosis with Lymphadenopathy in Children and Adults

Work on toxoplasmosis was started at the State Serum Institute when the first Danish case of congenital toxoplasmosis was diagnosed in 1948 at the University Department of Pædiatrics (Boesen). It then became clear that it was necessary to establish a serological-diagnostic service, and we had the opportunity of learning the dye test in Stockholm at Gard's laboratory—this reaction being later standardized by Aagaard—and were made acquainted by Sabin with the technique of the complement-fixation test. When further cases were diagnosed, a thorough study of the disease was undertaken in close co-operation between specialists in the various medical disciplines of the University, Blegdam Hospital, the Third Department of the Municipal Hospital, and the Finsen Institute, and also between doctors in general practice, pathologists and veterinarians.

Clinical Manifestations

In addition to congenital toxoplasmosis, infection with *Toxoplasma gondii* occurs as an acquired disease with five clinical manifestations:

(1) *T. acquisita exanthematica* (Pinkerton and Hendersen, 1941)—a febrile, often fatal, disease with a universal typhus-like exanthema and with symptoms of pneumonia, myocarditis and involvement of the central nervous system. Post-mortem reveals cell infiltration and necrotic foci in heart, lungs and central nervous system, with toxoplasma-like structures in the myocardium in all cases.

(2) *T. acquisita cerebrospinalis* (Sabin, 1941).

(3) *T. acquisita ophthalmica*, characterized by a chorioretinitis (Jacobs *et al.*, 1954).

(4) *T. acquisita lymphonodosa*.—The first Danish case was reported in 1950 at the VIth International Congress for Pædiatrics in Zurich, and at the same time a case was published from Sweden by Gard and Magnusson (1951). In England, toxoplasmic lymphadenopathy was observed in 1954 by Skipper *et al.*, and by Cathie, and recently as a laboratory infection by Beverley *et al.* (1955).

Based upon our observations of patients from whom toxoplasma have been isolated from lymph-node biopsies, it is possible to divide the third form of the disease into three main groups:

(*a*) *A febrile lymphadenitis* (Table I, Fig. 1).—In the following case a significant rise in

TABLE I.—5 CASES OF TOXOPLASMIC LYMPHADENOPATHY WITH FEVER

Case	Age	Sex	Symptoms at onset	Temperature Max.	Duration	Preliminary diagnosis
R. P.	8	F	Tiredness; chill; catarrh;	40·2° C.	2 weeks	Fever of unknown origin,
A. B.	3	M	dry cough; diarrhœa (blood)	38·0° C.	3 weeks	gastro-enteritis, lymphadenopathy
I. R.	15	M	Tiredness; chill; tender cervical lymphadeno-	39·8° C.	2 weeks	Fever—infectious mononucleosis
T. H.	9	M	pathy	39·6° C.	2 weeks	Fever—leukæmia?
T. B.	6	M	Tiredness; fever	39·5° C.	4 days	Infectious mononucleosis

[1]*From:* The State Serum Institute. Director: J. Ørskov, M.D. This work was aided in part by a grant from the P. Carl Petersen's Foundation.

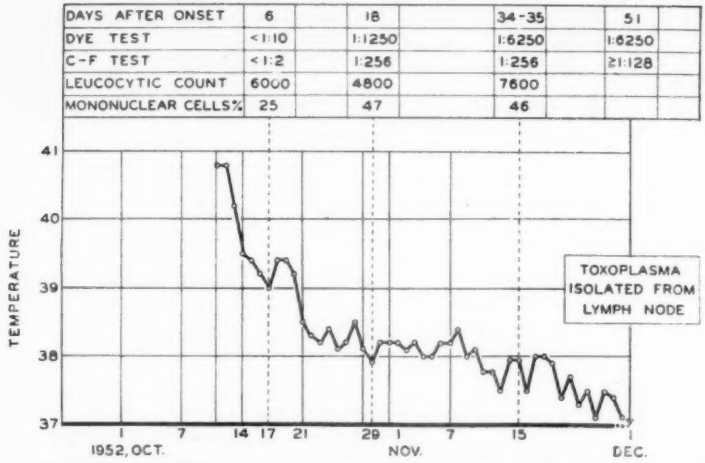

FIG. 1.—A febrile case of toxoplasmosis acquisita lymphonodosa in a 39-year-old man. Isolation of toxoplasma from an axillary lymph-node biopsy.

titre is demonstrated and the diagnosis verified by the isolation of toxoplasma from a lymph-node biopsy:

History.—Case No. 6022, Blegdamshospitalet, Epidemic Hospital of Copenhagen. A 39-year-old man, previously in good health, was suddenly taken ill on 12.10.52, with chills and temperature of 40·8° C. No symptoms, apart from moderate headache, tenderness in the back, and a slight angina.

On admission.—Five days later the general condition was remarkably unaffected; temperature 39·2° C., pulse 80. Except for some redness of the fauces and tender swelling of the left angular lymph node, there were no signs, and particularly no exanthema, no respiratory signs, no lympha-denopathy or enlargement of liver or spleen; there were no neurological signs.

Diagnosis.—Preliminary diagnosis: Tonsillitis; fever of unknown origin; infectious mononucleosis. Because of the demonstration of a relative lymphocytosis together with a negative Paul-Bunnell test, sero-reactions for toxoplasmosis were carried out on 3.11.52 with positive result (Dye test 1 : 1250); the reactions were negative on 17.10.52 (Fig. 1). Then an axillary and inguinal lympha-denopathy was revealed. The single lymph nodes, the size of hazelnut kernels, were tender, rather firm and discrete; no attachment to the underlying tissue; the covering skin unaffected.

Fifty-one days after onset of the disease a strain of toxoplasma was isolated from an axillary lymph node biopsy.

Laboratory findings.—Hæmoglobin value 95 → 83 → 99%. Sedimentation rates on October 20, November 13 and December 4 were 39, 58 and 34 mm. in one hour (Westergren). Leucocyte counts on October 17, October 29 and November 14: 6,000, 4,800 and 7,600 respectively. The differential counts on these dates were: unsegmented: 9%, 6% and 7%; segmented: 65%, 42% and 35%; eosinophils: 0%, 3% and 12%; large lymphocytes: 9%, 27% and 29%; small lymphocytes: 14%, 18% and 14%; monocytes: 2%, 2% and 3%. The large lymphocytes were atypical. Thymol turbidity test 0·23 (positive). Spinal fluid normal.

X-ray of chest.—No enlargement of hilar shadows.

X-ray of skull.—No intracerebral calcification.

Electrocardiogram.—Normal.

Course.—The temperature remained elevated for forty-three days. After fifty days in hospital the patient was discharged, complaining only of fatigue, which lasted for about four months. At follow-up examination six months later the patient felt completely well, but the lymphadenopathy was still present. Dye test 1 : 6,250. C.F. test 1 : 32 (64). No complications have been observed, except for a febrile retinopathy.

Treatment.—Penicillin 500,000 units for five days without any effect on temperature.

Source of infection: uncertain. The patient often eats raw meat and raw eggs.

(*b*) *A non-febrile form* where the enlarged lymph nodes are the only sign revealed by the patients themselves (Table II).

TABLE II.—3 CASES OF NON-FEBRILE TOXOPLASMIC LYMPHADENOPATHY

Case	Age	Sex	Symptoms at onset	General condition	Preliminary diagnosis
H. B.	3	F	None*	Unaffected	Lymphadenopathy
O. B.	13	M	Cervical lymph-adenopathy	Unaffected	Lymphadenopathy Lymphocytosis
H. P.	16	M	Tender cervical lymphadenopathy	Unaffected	Lymphadenopathy

*Typical toxoplasmosis in a brother.

(*c*) *A sub-clinical form*, the lymphadenopathy being found on routine serological examination or among contacts of verified cases.

The enlarged lymph nodes, varying in size from that of a hazelnut kernel to a walnut, are firm and discrete and usually painless, but they might be tender during the first weeks of the disease. They are found in the sub-occipital region, in the neck, the axilla and groin, and in some cases enlarged lymph nodes can also be demonstrated in the hili of the lungs. On microscopical examination, characteristic pathological changes are demonstrated (Siim, 1951; Bang, 1953). The covering skin is never affected and there is no attachment to underlying tissue. The spleen is seldom palpable.

In contrast to the exanthematic and encephalitic forms, the disease ran a benign course, all the patients having made complete recovery with no complications from the central nervous system, heart or eyes. However, in a girl of 3 years a lymphosarcoma developed later. The enlargement of the lymph nodes persists for more than six to nine months and in some of the cases convalescence was accompanied by pronounced tiredness.

Diagnosis.—The patients showed Sabin-Feldman dye test titres of 1,250 to 6,250 and C.F. titres of 1 : 32 (128), the reactions generally being positive after about a month, and remaining positive for more than six to twelve months. The Wassermann reaction and the Paul-Bunnell test were negative (Table III).

TABLE III.—SEROLOGICAL FINDINGS IN 8 CASES OF ACQUIRED TOXOPLASMOSIS

Case ..	R.P.	A.B.	J.R.	T.H.	T.B.	H.B.	O.B.	H.P.
Dye test titre	5,000	6,250	1,250	6,250	6.250	6,250	6,250	1,250
C.F. titre ..	128	—	32	64	128	128	128	64
Paul-Bunnell	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Wassermann	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

Evaluation of the serological reactions is difficult because (*a*) antibodies are found in apparently healthy persons, (*b*) the reactions remain positive for a long period, and (*c*) antibody formation can also follow a latent infection. Demonstration of increased titres alone in cases of uncertain ætiology can by no means be taken as proof that the actual disease is of a toxoplasmic nature. This can only be confirmed by the demonstration of a significant rise in titre in a new test simultaneously with the development of clinical features (Fig. 1).

With regard to the specificity of the sero-reactions, maximal positive titres in both tests should be considered specific because previously all verified cases of both congenital and acquired toxoplasmosis have been accompanied by strong positive reactions. On the other hand, positive reactions have never been found with regularity in any other disease entity of well-defined ætiology. However, the significance of low titres is still open to investigation.

Differential diagnosis.—The various diagnoses on admission have been: Fever of unknown origin; lymphadenopathy; tuberculous adenitis; infectious mononucleosis; leukosis; Hodgkin's disease; metastases (carcinoma of the breast, carcinoma of mediastinum); adenophlegmon; mumps.

Differential diagnosis from atypical mild cases of glandular fever will often present difficulties, but the markedly positive toxoplasma reactions will make the diagnosis of toxoplasmosis probable, and the demonstrations of the pathological changes will confirm that diagnosis. The fundamental difference in character of the two diseases will be clear from the fact that patients have been observed with typical serological, clinical and hæmatological features of glandular fever, and that toxoplasmosis has occurred later in these patients. The reverse has also been observed. It is important that in establishing a diagnosis of toxoplasmosis, the existence of a malignant disease can be excluded.

On *laboratory examination* the main clinical finding is a relative lymphocytosis with up to 60–80% lymphocytes, the large ones having an appearance somewhat similar to the McKinlay cells found in infectious mononucleosis. The hæmoglobin value is normal or slightly

decreased. The total leucocytic and platelet counts are normal and the sedimentation rate is normal or slightly increased. The thymol turbidity test may be positive in the febrile cases.

Isolation Experiments

Technique.—The lymph nodes are removed surgically, minced with scissors, and saline added to make a 1 : 5 to 1 : 10 suspension. 0·5 c.c. of this rather coarse suspension—not only the supernatant fluid—is injected intraperitoneally into stock mice in which latent infection has never been found. The infection only rarely kills the animals but most often runs a subclinical course. According to Aagaard's technique, the animals are killed after about six weeks and a dye test is performed on heart blood and sub-inoculations made from the brain.

As early as 1930 Bland reported that a strain had been obtained from a rabbit inoculated with blood from a patient with infectious mononucleosis.

Our first strain was recovered in 1952 and subsequently several strains have been obtained (Siim, 1952*a*, *b*; 1953) and also by Armstrong *et al.* (1953) and by Cathie (1954). The results of seven isolation experiments are shown in Table IV. Toxoplasma were demonstrated microscopically in the peritoneal exudate. The strains isolated cannot be distinguished, either morphologically or by staining techniques, from Sabin's strain RH. In cross-neutralization tests no differences could be demonstrated in the titres of various human and animal sera from human cases, and in protection experiments rabbits surviving infections with one of the strains isolated were immune to a challenge three months later with strain RH.

TABLE IV.—INOCULATION OF MICE WITH A LYMPH NODE SUSPENSION

Experiment No.	No. inoculated	No. of			Observation period in days	Positive dye tests	Isolation of toxoplasma
		Dead	Survivors	Sacrificed			
1	4		4		57	+	+
2	10		10		40	+	+
3	7		7		39	+	+
4	4			1 (14)			+
			3		38	+	+
5	4			1 (9)			+
			3		38	+	+
6	8		8		57	+	+
7	4	1 (13)		1 (11)		+	+
			2		52	+	+
Total	41	1	37	3			

Figures in brackets are the number of days after inoculation on which the mouse died or was sacrificed.

Pathogenesis.—The congenital infection is acquired *in utero* and therefore the mothers must have been infected before or during pregnancy, despite the fact that the majority of these mothers have apparently been healthy without any history of definite illness during pregnancy, and on post-natal examination no characteristic signs of disease have as yet been demonstrated. However, a case of toxoplasmic lymphadenopathy in the third month of pregnancy has been observed in a mother who later gave birth to a child with congenital toxoplasmosis, and a similar case has been reported by Farquhar and Turner (1949). The detection of acquired toxoplasmosis in pregnant women is still the only possible way of preventing the tragic cases of congenital toxoplasmosis in which the severe damage is irreparable and for which no specific therapy is yet known. Therefore, the most thorough examination should be carried out when pregnant women show evidence of inexplicable fever, lymphadenopathy or tiredness, and the safest course would be to advise that pregnancy be avoided in the acute stages of an acquired infection, where the possibility of toxoplasma being present in the blood might exist.

Epidemiological problems.—Toxoplasmosis occurs in warm-blooded animals in most parts of the world. The disease is reported not only in wild animals such as hares, rats and pigeons, but also in pet animals such as dogs and cats, and in domestic animals, e.g. pigs, cattle, sheep, rabbits and hens.

Although all reports on toxoplasmosis in animals have not yet been confirmed by isolation of the organism, there seems to be no doubt that warm-blooded animals are susceptible—at least all attempts to infect them experimentally have been successful. The widespread occurrence among animals living in the closest contact with man is of epidemiological importance, proving rich possibilities for infection, but at the same time making epidemiological studies extremely difficult. The following possibilities should be considered:

(1) Toxoplasma has been found in urine from rabbits and dogs; in fæces from dogs

with hæmorrhagic colitis; in superficial necrotic foci in spontaneously infected pigeons (Biering-Sørensen). Toxoplasma pseudocysts have been demonstrated in the ovaries of naturally infected hens (Biering-Sørensen), and it would thus seem possible that raw eggs might be infected. Toxoplasma is also present in milk and in the muscles of naturally infected animals.

(2) *The mode of entry* is not known, but it is possible to infect animals experimentally via the mucous surface of the eye and the upper respiratory tract, and by feeding, and toxoplasma has also been found to penetrate carefully shaved skin.

(3) *The mode of spread* is also unknown, but contamination of food and the ingestion of raw meat, milk and eggs from infected animals, and droplet infection, as well as transmission by blood-sucking animals should be taken into consideration.

(4) *Resistance of toxoplasma.*—Although it is known that toxoplasma are sensitive organisms which do not resist heat, desiccation, chemical compounds, &c., further experiments are necessary to elucidate how long toxoplasma can survive, for instance, in the meat of slaughtered animals. It is possible that the pseudocyst will exhibit a considerably greater resistance against the stomach-juice than the isolated organism.

Conclusion

(1) Toxoplasma has been isolated from patients with characteristic clinical, histological and serological findings.

(2) The isolated strain has been identified as *Toxoplasma gondii* (morphological, serological and pathogenic criteria).

(3) The disease has been reproduced in animal experiments.

(4) A significant rise in serological titres has been demonstrated in the acute stage of the disease.

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Professor C. P. Beattie (Bacteriology Department, Sheffield University):

Effects of Infection with Toxoplasmosis

Toxoplasma has little respect for the boundaries of zoological families or of geography. When so many living creatures are infected and when the parasite may be found in any of their excretions, secretions and body fluids, the possible sources of infection are obviously great. Yet we are woefully ignorant of how it is transmitted. Indeed the only method of which we are certain is the congenital, transplacental one. There must be others.

The alimentary route comes first to mind, particularly contamination of food or drink or suckling an infected dam; but it is really quite difficult to infect even the highly susceptible laboratory mouse by this route. The gastric juice tends to kill toxoplasma. In these animals cannibalism has proved the best method of alimentary infection, probably because the pseudocyst found in the tissues is more resistant than the crescentic form of the parasite. Quite possibly infection may spread among rodents in this way, and also to dogs and cats which prey upon them and on rabbits, an animal commonly infected. In this country it is unusual for man to eat uncooked meat; but contamination of fingers or of food after cooking remains a possible source. Bites have also been found to cause infection in animals

(Kåss, 1954) and in one instance a rabbit bite was thought to have produced infection in man (Sabin *et al.*, 1952).

It is easier to produce experimental infection of animals through the mucous membranes of the nose, vagina or conjunctiva. The vaginal route would not seem important as males are as frequently infected as females. More attention might well be paid to the possibility of respiratory infection, especially as the lung is often involved and toxoplasma has been found in tracheal mucus, in sputum and in saliva.

It is also possible that the parasite may pass through cracks or scratches in the skin and this may explain the higher proportion of reactors to the antibody tests in veterinary surgeons, slaughterhouse workers and, particularly, rabbit handlers.

More is known of the damage that toxoplasma does; in most cases it does little.

Toxoplasma has been isolated from apparently healthy rats and pigeons (Eyles, 1952; Jacobs *et al.*, 1952). It has been found in men who have died of other causes and has been isolated from the blood of a healthy young woman (Cole *et al.*, 1953). Very few, moreover, of the mothers who give birth to infected babies have any obvious illness during pregnancy. Even under the severe conditions of artificial inoculation animals may be infected and be shown to have a parasitæmia with little or no sign of illness.

Of course it sometimes does damage. This must depend, as always, on the two factors of the virulence of the parasite and the resistance of the host.

Variation in virulence of strains does occur, although it has not yet been proved that strains naturally occurring in a particular animal species vary in virulence for that species.

Resistance of the host plays a great part. It is likely that this in the ultimate analysis depends on antibody preventing the spread of toxoplasma from cell to cell. It may be, however, that the antibody which gives protection is something other than the antibody or antibodies detected in serological tests.

Many things contribute to resistance, whatever be its ultimate mechanism. The fœtus is particularly susceptible, while the mother, in most cases, escapes disease. Most commonly it is held that she contracts latent infection during her pregnancy; but Weinman's (1952) theory, that chronic latent infection acquired at any time is enough, cannot be ruled out. The fœtus he considers "a non-immune intruder into an environment where satisfactory balance has been established". Even here, however, the question of resistance comes into play. It is improbable that every fœtus of an infected mother is itself infected or even, if infected, develops signs and symptoms of toxoplasmosis. The frequency with which these appear in human twins seems greater than can be explained by the distribution of twins, and, just as at birth one twin is often the stronger, so one may show advanced signs of toxoplasmosis and the other, although infected, little or none.

In later life, both in other animals and in man, toxoplasmosis has been found to follow on some stress, such as cold, fatigue or captivity. Toxoplasma has been found in association with some other infection, such as bartonellosis, poliomyelitis, tuberculosis, meningitis, avian hepatitis. The 16 dogs in which Campbell (1955) found toxoplasma, all showed histological changes suggestive of concurrent distemper. In such cases there is probably a synergistic effect and the problem arises of which agent initiated the disease.

Of course toxoplasma can, and not infrequently does, by itself produce disease.

It is in man that the disease has been most studied. Here the congenital form is best known, manifesting itself in infancy and characterized by the association of any or all of the following signs and symptoms, chorio-retinitis, rash, jaundice, hepatosplenomegaly, internal hydrocephaly (which may be found in the presence of microcephaly), convulsions, mental retardation, intracerebral calcification and pneumonitis. It may be, however, that the commonest manifestation is chorio-retinitis, of congenital origin, first observed in childhood or, perhaps, sometimes acquired in later life.

A few cases of encephalitis acquired in later childhood and, in adults, of a typhus-like syndrome in which a maculo-papular rash, pneumonitis, encephalitis and myocarditis are prominent features, have been described.

It would seem, however, that the commonest manifestation of acquired toxoplasmosis yet known in man is lymphadenopathy of "glandular fever" type.

In dogs, as in other species the young are most susceptible. Congenital infection has been described leading to still-births, premature births or death at an early age (Chamberlain *et al.*, 1953). Older dogs are less susceptible. Experiments have shown that they can be infected and develop a parasitæmia without illness (Sabin and Warren, 1942). The acquired disease is varied in its manifestations.

Sometimes catarrhal signs (conjunctivitis, rhinitis and sinusitis) are present at the onset. Sometimes changes of behaviour are early noticed. The dog is fevered and loses appetite and weight. Dyspnœa is common and vomiting and diarrhœa due to gastro-intestinal ulceration may be present. Lymph glands are enlarged and inflamed, nervous excitability and terminal paralysis are not uncommon. Habegger (1953) states that the symptoms were predominantly pulmonary in 47%, alimentary in 31% and nervous (including ophthalmic) in 22%.

Less is known about toxoplasmosis in cats. In the few cases reported the signs and symptoms have not differed from those in dogs.

Only recently has toxoplasmosis been recognized in cattle (Sanger *et al.*, 1953). The infection can be transmitted congenitally and in the milk. Clinical signs in calves are said to be dyspnœa, cough, fever, tremors, depression and weakness. In older animals excitability is more common than depression.

In sheep encephalomyelitis has been recorded (Olafson and Monlux, 1942) and a condition suspected of being "circling disease" (Wickham and Carne, 1950).

In swine toxoplasma may give rise to pneumonia, lymphadenitis, colitis and hepatitis (Farrell *et al.*, 1952).

Outbreaks of toxoplasmosis have been recorded in fowls. The disease has assumed a chronic form with peri- and myo-carditis, ulcerating gastro-enteritis, pneumonia, encephalitis and chorio-retinitis (Erichsen and Harboe, 1953; Habegger, 1953).

In contrast to what is found in the lower animals, damage to the respiratory system does not appear to be a prominent manifestation in man. The cases in which it has been recorded have been severe, and other systems have been equally, or more, affected. Is it possible that we are missing cases where the involvement is mainly respiratory; atypical pneumonia, perhaps, or even rhinitis which is stated to be one of the early signs in dogs, and to be found in intranasally infected rabbits? (Kåss, 1954). Stomatitis and sore throat have preceded glandular enlargement in human cases. May they not sometimes be the sole manifestations? Conjunctivitis has been found in animals but rarely recorded in man (Ansari and Minou, 1948; Ström, 1951). Involvement of the gastro-intestinal tract, common in animals, is rare in man. This may be due to a different route of infection, but, none the less, further attention might well be paid to it. Bamatter (1946) and Wollheim (1952) report cases of enterocolitis. As parasitæmia is produced any organ may be involved. Toxoplasma may cause myocarditis. Hepatitis and splenitis are commonly present in neonatal cases. Myositis has been described. Care must, however, be taken not to assume too readily that because toxoplasma is found it is the cause of the clinical condition.

Those of us whose interests are in veterinary medicine might enquire further into toxoplasma as a cause of neonatal deaths, stillbirths or abortions and might look to see if involvement of the posterior chamber of the eye is really as rare as is said. It would be of value to discover how common toxoplasma infection is in domestic animals. As in man, antibody tests may provide epizootiological guides but these tests will have to be critically considered.

It seems likely that there may be greater difficulty in lower animals than in man. Non-specific reactions may be more numerous and specific reactions of lower titre. Cole (personal communication, 1953) states that dye-test titres in cattle are low. This, and the fact that outbreaks are confined to certain herds, may explain Feldman's (1953) failure to find antibodies in cattle sera. Jacobs and his colleagues (1952) found discrepancies in both directions between the isolation of the parasite and the presence of antibodies in pigeons and (Eyles, 1952) in rats.

It is likely, too, that different results will be found in different parts of the country. Beverley on examining the sera of 20 London cats found only one to give a titre in the dye test of over 1 : 8. Of 50 cats of uncertain origin used for experiment in the University of Sheffield, 9 gave titres of over 1 : 8, the highest being 1 : 32. On the other hand one cat which scavenged meat, including rabbit, from a butcher's shop and was associated with a case of human toxoplasmosis gave a titre of 1 : 200 and two cats from a farm, associated with two suspected cases of human toxoplasmosis of "glandular fever" type gave titres of 1 : 90. Another cat from the country also associated with a human case of toxoplasmic lymphadenopathy gave a titre of 1 : 120.

No toxoplasma antibodies were found in the sera of 37 dogs specially bred for virus research. Of 15 London dogs only 1 showed a titre of over 1 : 8, among 28 Sheffield dogs 13 had such a titre, 3 having titres of over 1 : 32.

In addition to the cat already mentioned, a dog belonging to the employer of the butcher's boy who had toxoplasmic lymphadenopathy was found to show a titre of 1 : 80.

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Dr. I. A. B. Cathie (The Hospital for Sick Children, Great Ormond Street):

The Laboratory Diagnosis of Toxoplasmosis

Isolation of toxoplasmata.—The ultimate proof of the diagnosis of any infection must be recovery of the causal organism, and toxoplasma has been recovered from almost every tissue in the body. There is a choice of animal to inoculate and mice and guinea-pigs, intraperitoneally, are the most convenient.

It is said that prolonged blind passage may be necessary before the parasite is seen, and it is probably for this reason that more attempts at isolation of toxoplasma from patients are not made. On the five occasions where we have isolated toxoplasma the parasites have been recognizable either in the first—primary—inoculation or in the first passage of ground-up spleen. When we have carried passaging farther we have not been able to isolate the toxoplasmata in any case. Wildführ (1954) in Leipzig, who has isolated toxoplasma 44 times, found it necessary in no case to passage more than three times. For practical purposes, therefore, more than three passages are unlikely to be fruitful.

In isolating a toxoplasma from a patient, how do we know that we have not isolated something else which looks like a toxoplasma? We have contented ourselves with putting up our newly isolated strains in parallel with our test strains for the dye test and with making complement-fixing antigen from the new strains and testing that in parallel with our old antigen. We also observe the biological behaviour of our new isolation in relation to the standard strain, but this is as far as we can go, as there appears to be no further means of identifying a toxoplasma.

Apart from the isolation of the parasite, there are four tests for toxoplasmosis: the rabbit skin neutralization test, the toxoplasmin skin test, the cytoplasm modifying antibody or dye test, and the complement-fixation test. Of these, the rabbit neutralization test has rightly been largely abandoned owing to the difficulty of obtaining repeatable results and also because of the possibility that the rabbit itself may contain traces of specific or non-specific toxoplasma antibody. The skin test with toxoplasmin has been used extensively since its introduction by Frenkel (1948), and in this country Fisher (1951) was able to show a remarkable tie-up between the skin test and the dye test or cytoplasm-modifying antibody test.

With the remaining tests I must postulate that for the diagnosis of *active* toxoplasmosis both the dye test and the complement-fixation test must be positive. This postulate is based on the observations I have been able to make on the clinical data sent to me with the thousands of sera which have been examined at The Hospital for Sick Children, Great Ormond Street. There are, naturally, anomalies, but whenever a reasonable clinical

diagnosis of toxoplasmosis has been made these two tests have both been positive, and we have never seen a positive complement-fixation test without the dye test being positive.

Dye test.—It has been shown in this country, and all over the world, that as the population ages so the dye test becomes more positive in it, so that by the age of 60 more than 50% of the population have a positive dye test; but what of the titres? Table I shows the titres in

TABLE I.—261 HEALTHY ADULTS WITH DYE TEST POSITIVE AND COMPLEMENT-FIXATION TEST NEGATIVE

Titre	Number
1 : 4	27 (10%)
1 : 8	66 (25%)
1 : 16	65 (25%)
1 : 32	71 (27%)
1 : 64	27 (10%)
1 : 128	3 (1%)

some cases where there was no clinical evidence of toxoplasmosis and where the complement-fixation test was negative, that is, where there was no serological evidence of active toxoplasmosis. Clearly titres up to 1 : 64 may be expected in the normal population and therefore a titre of 1 : 64 by itself as support of a diagnosis of toxoplasmosis has no more value than a positive Mantoux test in a patient of similar age in the diagnosis of active tuberculosis. Once titres of the dye test get into the hundreds it is most exceptional not to find support for them with a positive complement-fixation test, and therefore a titre of 1 : 128 is probably indicative of active toxoplasma infection, while a titre of 1 : 256 is strongly suggestive. We have, of course, isolated the parasite from cases where the dye test has only been 1 : 16; in these cases, however, the complement-fixation test has been strongly positive and it is the high dye-test titre without the complement-fixation test being positive which is difficult to interpret.

Non-specificity of dye test.—It is well known that the dye test is not entirely specific for toxoplasmosis, but such conditions as trichomonas infection, sarcosporidiosis and infection with *Trypanosoma cruzi* may give a positive toxoplasm dye test (Muhlpfordt, 1951; Awad, 1954). It is probably fair to ignore infection with trypanosomes in this country, but trichomonas and sarcocystis infections must be considered in the diagnosis of toxoplasmosis. With regard to trichomonas infection some of the patients whom I have been able to test have had a positive dye test to accompany their trichomonas infection but they have nearly all been adult females, and we are not sure if the positive dye test for toxoplasmosis is related to the trichomonas infection or if it is the normal finding in the adult population in this country. The complement-fixation test in trichomonas infections is not positive. Recently I have been able to examine the sera of four adult males with trichomonas infection, and they have had negative dye tests.

As to the possibility that dye tests in our population are caused by sarcosporidia, it is a fact that animals giving negative dye tests for toxoplasmosis, after infection with sarcosporidia, may undergo conversion and give positive dye tests. I have no knowledge to confirm or refute this observation in man, but I think that if sarcosporidiosis were very common in this country we should be aware of it.

Complement-fixation test.—Although the assaults on the specificity of the dye test have caused some doubt as to its precise worth, until recently the complement-fixation test, using egg antigen, has not been assailed. We have not found a very accurate tie-up between the dye test and the complement-fixation test, about 25% of all positive dye test sera having a positive complement-fixation test. Potentially, therefore, either the egg antigen as prepared to-day gives less sensitive results than does the dye test, or, as is more likely, the complement-fixing antibody appears later and disappears more rapidly than does the dye test antibody. We think that the complement-fixation test titre with egg antigen should be 1 : 8 to have much significance. We do not know precisely how to evaluate a titre of 1 : 4. I should say here that the antigen we originally made was standardized against a sample of antigen kindly supplied by Dr. J. Warren, and each new batch of antigen made over the last five years has been standardized to give the same results with known sera as the previous one.

Westphal (1951) in Hamburg felt some doubt about the sufficiency of sensitivity of the egg antigen and he has prepared an antigen by breaking up toxoplasma in animal peritoneal exudate with ultrasonic waves. With his antigen he found an 85% tie-up with the dye test (Westphal and Bauer, 1952) which suggests that it is a great deal more sensitive than our

egg antigen. Doubts, however, have been expressed as to the specificity of Westphal's peritoneal exudate antigen. Hein (1952) found that 59 out of 102 patients with tuberculosis gave positive complement-fixation tests with the Westphal antigen. More recently Kulasiri (1954) in Ceylon found that 49% of sera giving a positive Widal reaction to typhoid gave positive fixation with the Westphal antigen, while only 28% were positive when the Widal was negative. Both these workers considered either an anamnestic response or else a non-specific reaction to the Westphal antigen. It seems unlikely that this high proportion of positive Westphal antigen tests is caused by an anamnestic rise and we must therefore consider seriously that the Westphal antigen may be non-specific. There is always, of course, the possibility that tuberculosis and typhoid might predispose to the development of toxoplasmosis, but I would rather think that this modification of the ordinary toxoplasma antigen has led to non-specific results being obtained.

In defence of the egg antigen, through the kindness of Dr. E. S. Anderson at Colindale, I was able to test with the toxoplasma egg antigen some 45 sera giving positive typhoid Widal reactions. All these sera gave negative results, and four others I have been able to obtain from patients with typhoid fever gave a negative toxoplasma complement-fixation test. The egg antigen is not, therefore, under the same suspicion as is the Westphal antigen, and until shown otherwise I shall continue to regard it as specific.

Conclusion

I have indicated what titres we believe to be necessary for diagnosing active toxoplasmosis with the complement-fixing egg antigen and the Sabin and Feldman (1948) dye test. We have observed these titres in an infection rise and fall, the complement-fixing antibody eventually disappearing. Except where there is a congenital infection, or where there is a carry-over transplacentally, babies are born without toxoplasma antibodies. When they encounter toxoplasmata, therefore, and develop antibodies, at some stage titres will be lower than those we regard as diagnostic of active toxoplasma infection. Although we think a complement-fixation test titre of 1 : 8 is indicative of toxoplasma infection, we know that a positive complement-fixation test can revert to negative; at some stage therefore, as it falls from 1 : 8 to negative, the titre must be 1 : 4 and 1 : 2. We say as a rough and ready guide that these titres have no significance; obviously they do have significance, but we are unable to assess quite what worth to give to them and here, as in other serological investigations, it is obviously desirable to have paired or triple sera for the observation of antibody titre change. With a single isolated titre lower than those I have indicated we are quite unable to indicate to the clinician what meaning he should accord them and it is as important in toxoplasmosis as in any other condition to evaluate the family and clinical history as well as the laboratory findings in attempting to establish a diagnosis.

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Section of Anæsthetics

President—BERNARD JOHNSON, F.F.A. R.C.S.

[*April* 1, 1955]

DISCUSSION ON INDUCED HYPOTHERMIA

Dr. C. F. Scurr: Tissue anoxia due to circulatory arrest leads unless rapidly relieved to cellular death. The duration of anoxia necessary to kill cells varies: in the case of highly developed cells in the human brain a period of two to four minutes circulatory arrest leads inevitably under usual conditions to permanent cerebral damage. As a result, in cases of cardiac arrest the heart may be restarted by cardiac massage, but often because of delay, brain damage has occurred so that the patient never recovers consciousness. (In this connexion I am reminded that in one "cardiac-massage minded" centre across the water a framed notice hangs in the operating theatre which says in bold black letters, "As time flies, the neurone dies".)

If the body temperature be lowered cellular metabolism and oxygen demand are reduced, so that cells survive anoxia for longer periods. It has been shown in animal experiments that at a body temperature below 25° C., the circulation to the brain may be completely cut off for twenty minutes, and yet complete recovery may occur, there being no physiological or histological evidence of cerebral damage. It is of interest to note that at these low temperatures coronary occlusion was rapidly fatal, a reversal of the normal finding that the heart withstands anoxia better than the brain.

It follows from these observations that hypothermia might permit the performance of certain operations which would be impossible at normal temperatures owing to cellular death from anoxia.

Conditions in which a hypothermic technique might be valuable are:

(1) Intracardiac procedures requiring an open heart, with temporary occlusion of the venæ cavæ and *cessation of the circulation*—for example, repair of certain cardiac septal defects.

(2) Transposition of the great vessels—in which the operative treatment necessitates *circulatory occlusion*. The simple clamp and crossover operation has now been abandoned, however, owing to coronary artery anomalies.

(3) Operations for congenital cyanotic heart disease—although *circulatory arrest* is not as a rule *essential* in these cases, hypothermia reduces the oxygen demand and anæsthetic requirements: the safety margin may thereby be increased. The indication for hypothermia here is a relative one, the temperature need not be reduced to a very low level. Most of our series are in this group; I believe a number of cases employing a similar method have been operated on in d'Abreu's department at Birmingham (Inglis *et al.*, 1954).

(4) In intracranial procedures involving temporary arrest of the circulation to part of the brain. In this connexion it has been suggested that hypothermia might increase the margin of safety in induced hypotension for neurosurgical procedures.

(5) In certain abdominal and thoracic operations; for example, for aortic aneurysms, involving excision and replacement by graft or plastic tube. Under hypothermic conditions the kidneys and spinal cord can tolerate the period of circulatory arrest necessitated by the operation. Professor C. G. Rob has a very interesting series of such cases, the anæsthetic management of which has been described recently by Cheatle (at the Medical Society of London).

THE ADVANTAGES ACCRUING FROM THE HYPOTHERMIC STATE

(1) *Oxygen requirements are reduced.*—Provided shivering is prevented the oxygen consumption falls in a linear fashion with the reduction of body temperature. At 30° C. oxygen requirements are reduced to 55%, and at this level the B.P. is usually well maintained. At 20° C. oxygen consumption is approximately 15% of normal (Bigelow *et al.*, 1954). Lynn and others (1954) suggest that in dogs it would be approximately zero at 10° C.

(2) *Cardiac activity is reduced*—aerobic energy uptake and, to a greater degree, left ventricular work both decline (Edwards *et al.*, 1954).

(3) *Coagulation time is increased.—In vitro* at 20° C. it is approximately trebled (Macfarlane, 1948). Under hypothermic operation conditions there is a fall in the platelets which may seriously retard clotting and lead to post-operative hæmorrhage. To some extent these antithrombotic effects may be beneficial, as thrombosis is a well-known complication in certain types of cardiovascular surgery.

(4) *Anæsthetic requirements are reduced.*—It is reported that below 27° C. consciousness is lost, the hypothermia of itself inducing the anæsthetic state.

(5) *Harmful bacterial and enzyme activity is suspended.*

Dangers of the Method

(1) *The cold stress response* (Delorme, 1953) as manifested by endocrine activity and shivering; the latter gives rise to complexes which can be observed on the electrocardiographic record. At the start of cooling there is increased sympathetic action with associated release of adrenaline. Vasoconstriction results and tends to retard heat loss. There is increased production of ACTH and thyrotrophic hormone which tends to raise heat production.

The muscular activity involved in shivering leads to an increase in heat production and oxygen demand; this process can for a time prevent a fall in temperature in the initial stages of the cooling procedure. Shivering can and should be prevented by anæsthetics, by curarizing drugs and by chlorpromazine. This last agent is particularly effective in helping to lower body temperature, which it does by decreasing heat production in voluntary muscle, by producing vasodilatation and promoting heat loss, and possibly by an effect on the temperature-regulating centre. In addition to these effects chlorpromazine has a very wide spectrum of pharmacological activity, but it is not an essential agent in the hypothermic technique and has not, indeed, been used in the present series of cases.

(2) *Cold tissue injury.*—In methods involving surface cooling this can be prevented by avoiding extreme degrees of cold. It is unfortunate that infants may have a predilection for subcutaneous fat necrosis under these conditions because infant fat has a relatively higher melting point (Collins *et al.*, 1953).

(3) *Changes in the blood.*—(*a*) *Increased viscosity:* This occurs in the first place as a simple physical effect of cooling the blood, and secondly as a result of the hæmoconcentration which accompanies the induction of hypothermia. In cases of congenital cyanotic heart disease the blood is already very viscous (for example, the hæmoglobin may be 140%) and this effect is especially undesirable. Coupled with the vasoconstriction which accompanies cooling the increased blood viscosity leads to elevation in the peripheral circulatory resistance, so adding to the work of the heart.

(*b*) *A fall in the platelets:* This is especially marked in methods involving extracorporeal circulation of the blood. This effect may lead to serious post-operative hæmorrhage.

(*c*) *A fall in blood pH* (Fleming, 1954)*:* This is due to an increase in the amount of dissolved carbon dioxide (Cranston *et al.*, 1955). The solubility of carbon dioxide in blood increases as the temperature falls and this effect will tend to cause carbon dioxide retention. More important, however, is the fact that respiratory activity diminishes as the temperature falls. This fall in pH may be in part the cause of ventricular fibrillation, but it has possibly some slight compensatory advantage in promoting the dissociation of oxyhæmoglobin. This gaseous acidosis can be prevented completely by hyperventilation, which should therefore always be performed in these cases. Under conditions of hyperventilation the blood pressure (and so, presumably, coronary flow) is better maintained as the temperature falls, and experimentally survival to lower temperatures is possible before cardiac arrest occurs (Lynn *et al.*, 1954).

(*d*) The oxyhæmoglobin dissociation curve is shifted to the left: in other words, oxyhæmoglobin only dissociates at relatively lower partial pressures so that theoretically it is harder for the tissues to obtain oxygen; this is offset by reduced tissue oxygen demand and mitigated by any fall in pH. Experimentally the arteriovenous oxygen difference has been found to be within normal limits in cooled animals, and certain studies appear to show that the tissues can effectively utilize oxygen from the blood (Bigelow *et al.*, 1950*b*; Penrod, 1951).

(4) *The elimination of non-volatile anæsthetic agents* is greatly retarded; this is presumably due to the reduction in metabolism. As already noted, anæsthetic requirements are also reduced in the hypothermic state. Consciousness is lost at about 27° C., and respiratory arrest may occur at about 23°–25° C. Barbiturates and other respiratory depressants will predispose to respiratory arrest at relatively higher temperature levels. Because of these considerations drugs such as thiopentone and pethidine should be used in minute doses and post-operative sedatives should be given in reduced dosage. The metabolism of glucose is also retarded during hypothermia; Wynn (1954) has reported a blood sugar level of over 1,000 mg. per 100 ml. during hypothermic anæsthesia. For this reason a glucose solution should not be used for the intravenous drip.

(5) *The cardiovascular system.*—As the body temperature falls the heart-rate, cardiac output and blood pressure all decrease. For example, in dogs at 20° C. the cardiac output may be only 15% of normal (Bigelow *et al.*, 1950*a*). In proportion the blood pressure falls less than the other two factors. The mean arterial pressure is the product of the cardiac

output and the peripheral resistance, and although the cardiac output falls with the temperature, the peripheral resistance is increased, as already noted. As a result the reduction in blood pressure may be only slight until 30° C. or less, but it may then fall sharply as the temperature is reduced towards 25° C.

After an initial acceleration when cooling begins the heart-rate decreases in a regular and linear fashion as the temperature is reduced; at temperatures below 25° C. in man ventricular fibrillation may occur abruptly. The pulse shows a linear fall in rate, which is *not abolished* by vagal paralysis and is therefore presumed to be due to a direct effect upon the pacemaker (Burton and Edholm, 1955).

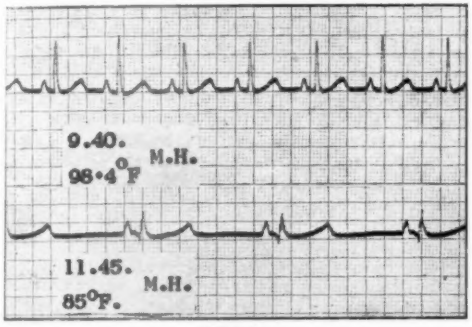

FIG. 1.

A bradycardia of 30 per minute is commonly encountered during operations under hypothermic conditions. At normal temperatures such slowing would be produced at the expense of an increase almost entirely in the diastolic phase. Under hypothermia the systolic phase is increased, in other words, the process of cardiac contraction is slow.

The electrocardiographic tracings shown in Fig. 1 (M. H.) demonstrate these changes: rate above is 100; rate below after cooling is 40.

As the temperature falls to critical levels cardiac irregularities may occur. Therefore electrocardiographic control is essential throughout these procedures. Cardiac irritability appears to be increased, and direct surgical stimuli may thus initiate ventricular fibrillation (Lynn *et al.*, 1954; Swan, 1954).

As further cooling takes place spontaneous ventricular fibrillation or cardiac standstill occurs and is the cause of death in progressive hypothermia. Dogs appear more prone to develop this condition than human beings. There is a great species variation in the temperature level at which this complication is encountered; in rats it may not happen until 12° C. (*Lancet*, 1954) but in adult man it is likely to occur around 25° C. Fortunately infants and young children are more resistant than adults in this respect, and it is in these young patients that the method at present finds its greatest applications. In those with acquired heart disease (for example, previous rheumatic disease) the liability to ventricular fibrillation is said to be increased and the method is probably contra-indicated in such patients (Bailey *et al.*, 1954).

The exact cause of ventricular fibrillation associated with hypothermia is imperfectly understood. Lange *et al.* (1949) blamed anoxia and reported amelioration with high oxygen tension. Some workers suggest that the fall in pH is responsible (Fleming, 1954) and it has been reported that hyperventilation has a protective effect (Lynn *et al.*, 1954; Fleming, 1954; Swan *et al.*, 1953*a*). On the other hand, there have been reports that a sudden fall in an abnormally high blood carbon dioxide can be a fibrillatory stimulus in the dog (Swan *et al.*, 1953*a*; Miller *et al.*, 1952). Ionic changes may be implicated but the evidence is contradictory—Sealy *et al.* (1954) suggested that post-hypercapnic ventricular fibrillation is due to increased serum potassium; improvement resulted from giving sodium and glucose. By contrast, Swan (Swan *et al.*, 1953*b*; Zeavin *et al.*, 1954) reported a *fall* in serum potassium during cooling and used potassium chloride to *arrest* fibrillation in the cold heart, pointing out that much intracellular potassium was lost from the myocardium during fibrillation (Sealy *et al.*, 1954). Recently Melrose (1955) reported an increase in the Ca/K ratio, and noted that injection of calcium ions produced a spike at the S wave of the electrocardiogram which was a precursor of ventricular fibrillation: conversely, Swan *et al.* (1953*a*) have used calcium chloride successfully to treat cardiac arrest in a hypothermic patient. Another suggested cause is that during hypothermia acetylcholine production is depressed, so that, the pacemaker losing its dominance, ectopic foci tend to arise. In keeping with this Swan (1954) reported that Prostigmine had a powerful protective effect, but he ascribed it to the potentiation of potassium flow across the cell membrane.

It is of interest to note that hibernating animals can be cooled to 4° C. (Burton and Edholm, 1955; Juvenelle, 1954), a temperature which, in the non-hibernator, would certainly lead to ventricular fibrillation, and, as stated above, infants withstand cooling much better than adults; on this evidence it seems likely that the main basic cause of fibrillation is connected with the qualities of inherent cardiac rhythmicity and conductivity. It is possible

that drugs may be developed—e.g. Benodaine (Cookson *et al.*, 1952; Sealy *et al.*, 1956)—which will prevent this complication arising.

Should ventricular fibrillation occur cardiac massage is undertaken, and when the heart muscle is seen to be well oxygenated, defibrillation is attempted by means of repeated brief electrical shocks of 1·5 to 2·0 amps. Brewin (1954) has recently advocated the injection of 1 ml. of 1 in 3,000 adrenaline into the ventricular cavity followed by massage; when cardiac tone improved a single 1/5 second electric shock of 1 amp. was given: after a short pause a co-ordinated beat reappeared.

Potassium and calcium solutions have also been used with success, Swan using potassium chloride to arrest fibrillation and following with calcium chloride to restart the heart. On occasion an artificial pacemaker may be useful.

It follows from this review of the hypothermic heart that continuous electrocardiographic control is an essential part of the technique. A sinus bradycardia with normal complexes has usually been seen in our cases. A bundle branch block may occur, A.V. block and ventricular extrasystoles are regarded as danger signals.

(6) *After-cooling*.—In the rewarming period "after-cooling" may occur; this is presumably due to opening up of the circulation in the very cold outer shell of the body (Burton and Edholm, 1955). Very cold blood from the periphery thus enters the main circulation. This further fall in central temperature may lead to ventricular fibrillation and death. It is obvious that the danger of this "after-drop" will be greater in methods involving surface cooling than in extracorporeal cooling of circulating blood. The fact that temperature gradients can be set up in the body raises the question as to the best site at which to assess the body temperature. Most workers have hitherto observed the *rectal* temperature by means of a thermocouple: it is obvious that the cardiac temperature is of the greatest importance and pharyngeal or œsophageal temperatures are probably more reliable guides to the degree of cooling. With regard to the rewarming process, experimental work shows that this should preferably be as rapid as possible, for example, by immersion in a hot bath or by means of an inductothermy apparatus.

(7) *Limit of time available*.—The studies on the heart imply that at the present time 25° C. is about the lowest temperature that can be safely induced. This factor limits the time available for circulatory arrest if anoxic sequelæ are to be avoided and Bigelow *et al.* (1954) have tabulated the period of circulatory interruption and the body temperature likely to be required for various operations. Bailey *et al.* (1954) have reported a case of complete circulatory interruption for twenty-two minutes at 21·6° C.; there was no evidence of cerebral damage thirty hours after the operation. Rob has described an operation under hypothermia in which occlusion of the thoracic aorta for two hours was followed by definite but minimal spinal cord damage.

Methods of Inducing Hypothermia

(1) *Surface cooling*.—The patient may be immersed in a bath of cold water or merely covered with wet sheets and cooling promoted by means of electric fans. At Westminster Hospital a special cooling blanket is used to cover the patient. Water at a temperature of 2–4° C. is circulated through tubes incorporated in the blanket (Scurr, 1954; Inglis *et al.*, 1954).

(2) *By circulating* blood from an artery (e.g. subclavian or femoral) through a long plastic tube immersed in a cooling mixture and returning the blood into a vein (saphenous) (Delorme, 1952). In other centres a vein-to-vein circulation incorporating a pump has been used (Ross, 1954).

Surface cooling methods are in general slower in action and more liable to the dangers of cold injury, of shivering and the development of thermal gradients, and overshoot; it is also said that metabolic changes and hæmoconcentration are more marked. This technique is however, simple and avoids cannulating an artery with the attendant threat to a limb; in small infants the cannulation may be a difficult undertaking and in such cases surface cooling is obviously to be preferred.

Extracorporeal cooling is more rapid and also saves time by enabling cooling to proceed *pari passu* with the opening of the chest (or even after the chest has been entered). In this way the total duration of cooling is reduced and cardiac massage is immediately possible should it be necessary. However, this rapid cooling may increase the tendency to ventricular fibrillation; and, furthermore, platelet loss due to extracorporeal circulation may predispose to troublesome hæmorrhage.

Description of Technique

At Westminster Hospital hypothermic anæsthesia has been undertaken in a number of children for various operations as shown in Table I.

TABLE I.—OPERATIONS UNDER HYPOTHERMIC ANÆSTHESIA

Initials	Age years	Age months	Age weeks	Operation	Lowest temperature during operation °C.
J. M.	4	11		Blalock's	23
M. S.	2	2		Blalock's	24
A. M.	1	5		Blalock's	25
W. M.		6		Blalock's	24·5
D. G.		6		Thoracotomy—investigation—pulmonary valvotomy	23
M. D.	2	2		Division of large patent ductus (window)	23
L. P.	6			Thoracotomy—attempted pulmonary valvotomy	23
T. L.			6	Removal of œsophageal cyst	28
R. S.			7	Ligation of patent ductus	25·5
K. C.	3			Thoracotomy for pulmonary valvotomy	25·5
M. H.	9	4		Pulmonary valvotomy	29
G. C.	13			Pulmonary valvotomy	28

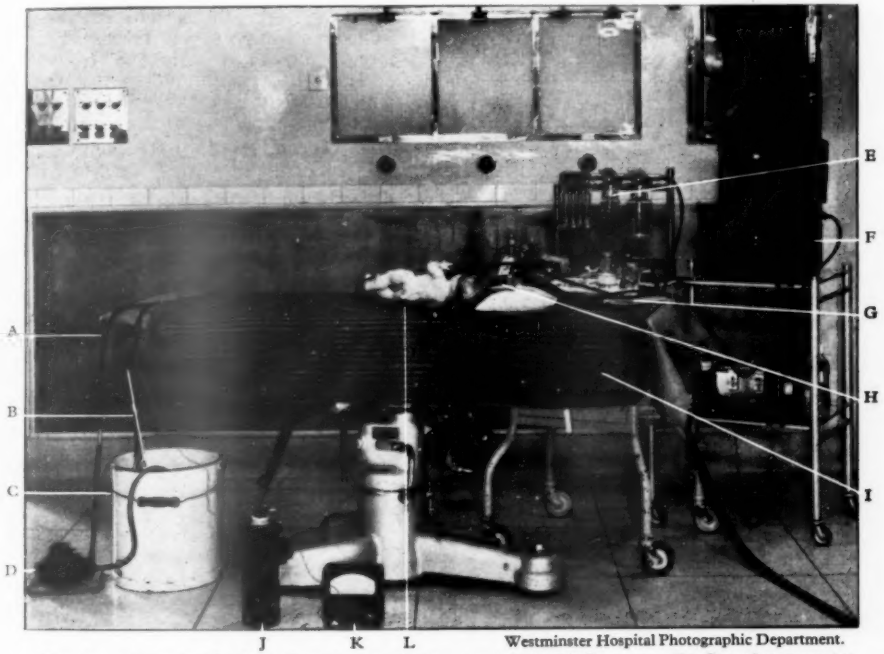

FIG. 2.—Apparatus for hypothermic anæsthesia. A.—Blanket inflow. B.—Outflow thermometer. C.—Reservoir. D.—Pump. E.—Anæsthetic machine. F.—ECG apparatus. G.—Breathing bag. H.—CO_2 absorber. I.—"Freezing blanket". J.—Zero junction. K.—Galvanometer, and L.—Rectal junction: thermocouple.

The apparatus used is as shown in Fig. 2, the child is anæsthetized and intubated in the usual way and then placed on the cooling blanket. The thermocouple and electrocardiographic leads are attached and an intravenous drip is set up. The blanket is then closed and the circulation of cooling fluid is continued. Light anæsthesia is maintained, e.g. with cyclopropane or ether and *oxygen*, or thiopentone gas and oxygen with relaxant so as to prevent shivering. The child's temperature falls as shown in Fig. 3 recording the course of a Blalock's operation in a child (J. M.) aged 5 years.

At 27° C. the anæsthetic may be discontinued and 100% oxygen used for the inflation. Shortly afterwards the operation is begun, relaxants being given as necessary during the thoracotomy.

The following points are noteworthy:

(1) The pulse falls in this instance to between 30 and 40 per minute. Continuous electro-

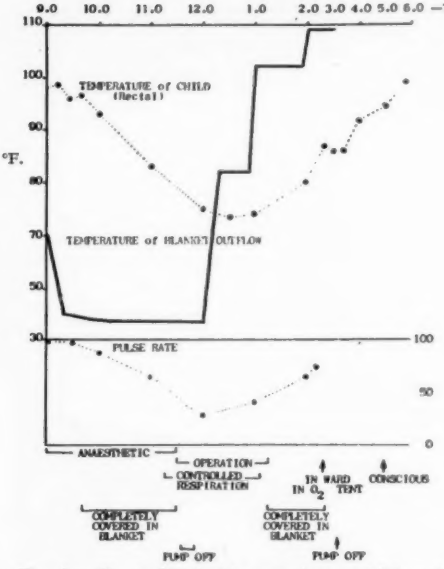

FIG. 3.—Chart of Blalock's operation on child aged 5.

cardiographic control was used and no serious cardiac abnormalities were seen despite the bradycardia which is probably less disturbing than the severe tachycardia common in these cases when conventional anæsthetic methods are used.

(2) At the start of cooling there is usually some apparent increase in respiratory activity. Later respiratory depression occurs—the temperature at onset of respiratory arrest varies, being higher in direct proportion to previous administration of respiratory depressant drugs. During emergence respiratory activity usually returns at a lower temperature level than that of apnœa during cooling. During cooling adequate controlled respiration should be started as soon as respiratory depression becomes evident. It is worth noting that the pupils are very widely dilated throughout the hypothermic period.

(3) Despite cessation of the pump and even substitution of warm fluid in the blanket the child's temperature continues to fall for half an hour or so. If this is not borne in mind the desired level may be overshot. This drift is worse after rapid cooling by immersion in a bath.

(4) These cyanotic babies as a rule become pinker when cooled. Estimations of arterial oxygen saturation confirm this observation as shown in Fig. 4. It is a great advantage to be able to inflate them with 100% oxygen. The reduced metabolic demand for oxygen must be balanced against reduced oxyhæmoglobin dissociation at low temperature. The balance is probably favourable to the method.

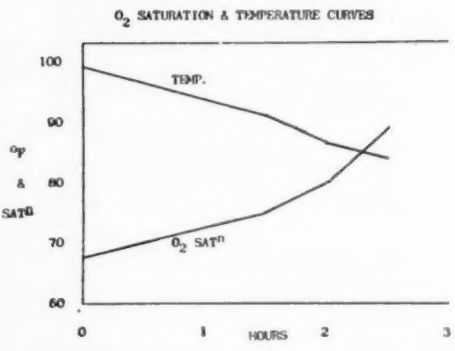

FIG. 4.—Case G. C., showing improvement in oxygen saturation with fall in temperature (arterial blood specimens estimated by hæmoreflector).

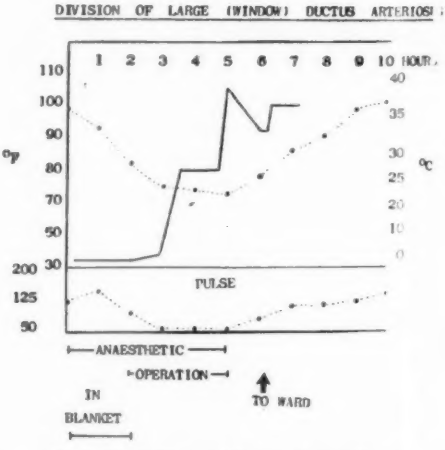

FIG. 5.—M. D., aged 2 years 2 months; weight 18½ lb.

(5) Reduced bleeding in the operative field is not a marked feature of this method—as noted, coagulation may, indeed, be retarded. Details of a similar case are shown in Fig. 5.

(6) The simplicity and rapidity of producing hypothermia by surface cooling and the improved operative course have made us prefer this method for infants and children with congenital cyanotic heart disease. In cases involving deliberate circulatory arrest hypothermia is essential. Hypothermia may well be a valuable adjunct to the use of the mechanical heart-lung.

In closing I should like to thank Dr. I. W. Magill for stimulating us to construct our first improvised cooling blanket after he had seen a transposition operation performed under hypothermia (Magill, 1953). I am also grateful to Dr. B. Cookson who visited us at the start of this work and gave us much helpful guidance. Finally, I am indebted to Mr. Charles Drew, the surgeon whose cases these were, and to Dr. J. R. E. Jenkins, my registrar, for his invaluable technical assistance.

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Dr. T. Cecil Gray:

Introduction.—The series of cases which I shall discuss have been collected by 7 anæsthetists working in association with my Department and I am grateful to them for enabling us to "pool" all our resources in order to get a clearer idea of our present position.

Over 110 cases have been collected in less than three years, with a further 20 that I can add. This number would seem to be a very eloquent reply to those who suggested in the past that we had been using this technique on occasions when there has been little justification.

With any new advance or method, the information that is sought, apart from the basic information which has been given us by Dr. Scurr, is: I, the method employed, II, the results which have been obtained, and III, its indications. I hope to answer these questions in the main.

I. Method

All our cases have been cooled by the surface technique. Of extra-corporeal cooling I have no experience, although I believe that it is a technique which carries its own risks which may prove in time to outweigh any advantages. The technique of cooling infants has been amply described by Dr. Scurr. Of the adults, for the first 40 cases in this present series we followed the French technique using the chlorpromazine-Phenergan-pethidine mixture although eliminating the use of a host of other drugs which were employed across the Channel. We found the technique unsatisfactory in that the period of cooling was prolonged

and the freedom from shivering was far from certain. Our present technique was devised by Dr. J. W. Dundee, and we have found it satisfactory. It is reasonably predictable, avoids shivering completely, and permits the required fall in temperature to occur in an average of one-and-a-half to two hours.

The basis of the technique is the use of extremely light anæsthesia and moderate dose of chlorpromazine to prevent shivering and vasoconstriction. Light anæsthesia alone, even with curarization, we have not found to give such satisfactory results.

The night before operation, the patient is given 50–100 mg. of chlorpromazine by mouth. One-and-a-half hours before cooling is to commence, 50 mg. of chlorpromazine is given intramuscularly with Hyalase; this may be combined, if the patient is unduly apprehensive or nervous, with 50 mg. pethidine or Phenergan to provide sedation. It is remarkable that, although we have given over a thousand of these intramuscular injections of chlorpromazine, we have not had a single instance of severe reaction or abscess formation despite the highly irritant properties of the drug. One-and-a-half hours later, anæsthesia is induced, in the case of abdominal and thoracic surgery with a dose of d-tubocurarine chloride of the order of 30 mg. and thiopentone 150–200 mg., and maintained with nitrous oxide and oxygen. An electrode from a thermocouple is inserted into the rectum, or, if that is inconvenient, into the œsophagus and a further electrode placed on to the skin, usually on the forehead. The cooling is brought about either with some form of blanket through which iced water can be circulated or for my own personal cases I have simply used ice packs. The ice bags must be applied all round the patient as cooling of the ventral surface alone results in considerable delay. The purpose of the skin electrode is to enable us to compare the rate of cooling on the surface with that in the body cavities. If the surface temperature is falling more rapidly than the rectal temperature, we would regard that as due to vasoconstriction and as an indication for the administration intravenously of 10–20 mg. of chlorpromazine. Only small amounts of chlorpromazine are required.

A further refinement of technique has been the changing of the patient's position every fifteen minutes in order to lessen the possibility of the pooling of cooled blood in any one part of the body with the aim of reducing the amount of after-drop of temperature. "After-drop" is the fall of temperature which takes place after the application of ice has been stopped and is no serious disadvantage provided it is remembered that it occurs. Fig. 1 shows the degree of after-drop in 37 neurosurgical cases. As can be seen it varies from 0° to 3·5° C., and depends on the type of patient. The well-built or obese have a pronounced "after-drop" and will cool slowly, whereas the lean, thin or emaciated patient cools rapidly and has no further fall in temperature after cooling is stopped. Children are a dangerous exception to this general rule in that they cool rapidly and usually have a pronounced after-drop. This can lead to trouble and it is doubtful whether it is safe to cool children unless there is some readily available method of warming them up quickly in case of too pronounced a fall in temperature. There will be other factors, of course, which will influence the amount of after-fall of temperature such as the room temperature and the degree of vasodilatation, but there is no doubt that build and age are of great importance in making the estimation as to when to stop cooling (Fig. 2).

II. Results

This series (Table I) has been collected by 7 anæsthetists over a period of three years, and

Table I.—Cases Operated under Hypothermia 1953–55.

Intrathoracic	Mitral valvotomy	1	
	Coarctation of aorta	1	
	Aortic aneurysm	1	
	Congenital cardiac	6	9
Neurosurgical	Vascular lesions	17	
	Tumours	22	
	Miscellaneous	2	41
General surgery	Total cystectomy	7	
	For portal hypertension	8	
	Œsophageal obstruction	5	
	Gastrectomy	6	
	Intestinal obstruction	2	
	Colectomy and abdomino-perineal	5	
	Pelvic evisceration	1	
	Others	12	46
Therapeutics		14	
	Total of series	110	

consists of 110 patients to which one could add a further 20 neurosurgical cases which have been treated since this Table was drawn up. Before considering these cases in greater detail according to their indication, I will review the complications.

Firstly, *the non-fatal complications*—we have had one inhalation of vomitus which was a case anæsthetized with the "lytic cocktail". A junior anæsthetist had not appreciated that the patient who was so sedated, might, if he had pyloric obstruction, regurgitate his stomach contents. He recovered after bronchoscopy. We had one burst abdomen; 3 cases had skin burns due to burst ice bags and direct contact of the ice with the skin, 2 had venous thrombosis in the arm due to the use of undiluted chlorpromazine, 1 temporary anuria lasting for three days, and 3 temporary auricular fibrillations. The auricular fibrillation occurred in elderly patients, commenced in the region of 34° C. and continued as the temperature fell to 30° C. The irregularities continued until, during rewarming, a temperature of 34° C. was reached when normal rhythm was restored. This occurrence in old people we would not consider as an indication to stop cooling.

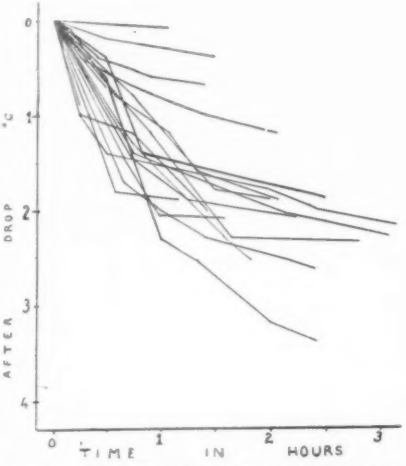

FIG. 1.—This shows the degree of "after-drop" in 37 neurosurgical cases.

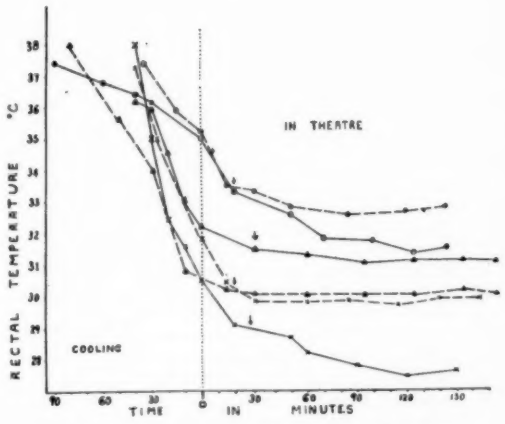

FIG. 2.—"After-drop" in three varieties of patients. ○=2 well-built or obese. ▲=2 thin patients. ×=2 children. The dotted line indicates the time of removal of ice bags. The arrow indicates the commencement of the operation.

Secondly, *the deaths* we think may be associated with the cooling are listed in Table II.

TABLE II.—DEATHS

Pulmonary	? Bronchopneumonia (hæmatemesis)		1
	Pulmonary embolus	(2*)	3
Cardiovascular	Ventricular fibrillation		1
	Cardio-pulmonary insufficiency		4
	Heart block (cerebral hæmorrhage)		1
	Cardiac failure and peritonitis		1
	Continued hæmorrhage (? transfusion reaction)		1
Others	Paralytic ileus and peritonitis		1
		Total	13

There have been 3 cases of pulmonary embolus. This might be regarded as particularly threatening because 2* of these cases were neurosurgical and this is a complication never seen in neurosurgery. They were, however, both patients who had been kept refrigerated for some days in the post-operative period because of extensive brain trauma during the operation. The one case of ventricular fibrillation occurred in the only patient with rheumatic myocardial damage. 4 cases labelled cardiac and respiratory insufficiency were neurosurgical patients who collapsed post-operatively. The case who died from hæmorrhage was definitely a hypothermic death. This patient had a porta-caval anastomosis. He had severe liver damage, and his coagulation time was so much increased at low temperatures

that he bled to death in spite of continued transfusions. The case of peritonitis died of paralytic ileus following a total cystectomy and transplant of the ureters. Ileus in total cystectomy cases has proved a hazard of the operation, but, except for this patient, death has occurred a considerable time after operation, and we have no evidence that cooling has predisposed to this complication.

III. Indications

We have classified our series under headings according to the indication for this type of anæsthesia.

A. *Intrathoracic.*—This group in our series is small because we believe that the majority of children with ordinary congenital cardiac defects can be operated upon with conventional forms of anæsthesia. Cooling is, in our opinion, only indicated where circulatory arrest must be achieved or perhaps, in extreme cases of Fallot's tetralogy in which cardiac failure is present or imminent. Our experience with open heart operations has so far not been encouraging and of the 13 deaths of the series, 5 have occurred in this group. In rheumatic heart disease, hypothermia may well be contra-indicated. One seriously ill patient for mitral valvotomy was cooled at the surgeon's request in the belief that lowering the temperature would improve the patient's oxygenation. As the temperature fell, the heart action became feeble and on opening the chest the heart was seen to be greatly dilated and beating sluggishly. Dilatation of the valve at a temperature of 25° C. resulted in irreversible ventricular fibrillation. Experiments which we have been able to carry out with the Starling heart-lung preparation in dogs, may have some bearing on this case. Under conditions of constant peripheral resistance in this preparation the cardiac output is maintained as low as 20° C. Starling found this to be the case only to 28° C. As there is bradycardia at low temperatures, the maintenance of output is due to an increasing stroke volume. However, these experiments have also shown that when the venous return to the heart is increased at low temperatures in adult dogs, the myocardium loses its power to compensate by increasing the stroke volume, so that at high venous flows the cardiac output is not maintained. This would seem to indicate that at temperatures below 30° C., there is interference with the efficiency of the heart muscle. Starling's "Law of the Heart" no longer applies. It would seem reasonable to expect that this myocardial "damage" would be much more serious in its significance in diseased states, as for example in rheumatic disease. It is interesting that the puppy's heart maintains its power to compensate for an increasing venous return even as low as 20° C.

B. *Neurosurgery.*—Patients who require prolonged hypotension to facilitate or permit neurosurgical procedures, particularly if they have to be operated upon in the semi-upright position, will obviously benefit from hypothermia. Our neurosurgical unit has had some remarkable results in the treatment of vascular tumours and aneurysms of the brain and Mr. C. B. Sedzimir has been able completely to occlude the middle cerebral artery for periods up to twenty minutes without producing apparent cerebral damage.

C. *Therapeutic indications.*—This particular series includes 2 cases of thyrotoxicosis, the remainder being patients in whom there has been severe cerebral damage accompanied by œdema and/or hæmorrhage. Where cerebral anoxia might be prolonged or perpetuated by cerebral œdema, reduction of the oxygen demand of the brain is indicated and our experience has shown that such patients benefit by reduction of temperature. Of the 2 cases of severe thyrotoxicosis, one was in crisis and the other had been presented for operation on two previous occasions but had been returned to the ward because of the circulatory condition. Both responded well to hypothermia.

D. *General surgery.*—In general surgery, I consider there are two indications for hypothermia. The first of these is when some degree of hypotension is required in patients for whom lowering of the blood pressure at normal temperature would be considered hazardous. An example was an old man of 72 who had a bilateral inguinal hernia which extended down to knee level. He had been bedridden for six months, was œdematous, had marked arteriosclerosis but was otherwise cheerful and willing to undergo anything to make his lot more tolerable. Unfortunately, no blood could be found with which he was compatible and as his hæmoglobin was only 65%, it was clear that some measures would have to be taken to reduce the blood loss in what promised to be a vascular and hæmorrhagic operation. He was operated on under hypothermia and is now ambulant and living a reasonably normal life (Figs. 3 and 4).

My second indication for hypothermia in general surgery, which I put forward very tentatively, is to protect the patient against the aggression of surgery as manifested by that syndrome which for years has been labelled "shock". A great deal has appeared in the literature drawing attention to the excellent condition of patients who have undergone very extensive surgery under so-called "artificial hibernation". The time has surely come

FIG. 3.—Before treatment.

FIG. 4.—After treatment.

to cease using this term. There are two entities. One is the depression of various autonomic reflexes and responses by drugs such as, for example, chlorpromazine, and the other is a reduction of metabolism by hypothermia. It is a combination of these two as practised by French schools, which has been labelled hibernation, although it bears only the most distant relationship to the hibernating animal in which there are extensive endocrine readjustments.

There is undoubtedly a widespread impression among clinicians that patients who are submitted to these techniques are in some way "stabilized" so that, provided their blood loss is replaced, surgical trauma produces no apparent change in their circulatory condition. How difficult it is, however, to demonstrate objectively such an indefinable entity as "protection from shock."

In an attempt to find some objective evidence to refute or support this clinical impression, we have initiated a programme of observations of which we are only at the moment on the threshold. Our object is to discover whether or not the recognized responses of patients and animals to the stress of operation might not provide us with the necessary yardstick with which we could compare patients under hypothermia with those under the conventional forms of anæsthesia. In this we have been lucky enough to be assisted by Mr. Ian MacPhee of the Department of Surgery.

A first approach was made in the clinical field to investigate the changes in blood eosinophil counts and electrolyte balance which, it is believed, reflect the responses of the adrenal cortex to injury. Observations of hypothermic patients revealed no difference in their eosinophil response to operation and the electrolyte changes after operation were identical with those described by Moore and Ball (1952) and MacPhee (1953) under conventional anæsthesia. A little thought led us to believe that this was perhaps only what might be expected. The changes in electrolyte excretion are a reflection probably of the outpouring of steroids, particularly aldosterone, from the suprarenal cortex which occurs as a result of ACTH secretion by the pituitary gland. These endocrine secretions are "fired off" by the "stress" of the operation. But this reaction could also be initiated in the recovery period, even if it were suspended at the actual time of operation by our anæsthetic technique. In fact there is evidence (MacPhee, 1955) that the very anticipation of an operation is sufficient to fire off these hormonal activities and produce changes in electrolyte excretion. It seemed to us, therefore, that we must turn to animals if we desired to discover whether hypothermia was affecting this particular response to operation.

We, therefore, undertook to observe the electrolyte and steroid responses in dogs who were operated on under hypothermia and who were maintained hypothermic for the minimum of three days, which period is required for the changes to be manifested. If during these three days characteristic changes in electrolyte excretion occurred and the total steroid

output from the suprarenal cortex increased, then we could conclude that our technique was providing no cover, but if, on the other hand, these changes did not occur or seemed to be modified then we were doing something which might well be beneficial to our patients.

We have so far been able to undertake seven such experiments in dogs. In these dogs we have measured the total steroid output in the urine every twenty-four hours as well as changes in serum and urine electrolytes. I do not wish to describe the details of these experiments here but Fig. 5 shows the results in one of these dogs and demonstrates that,

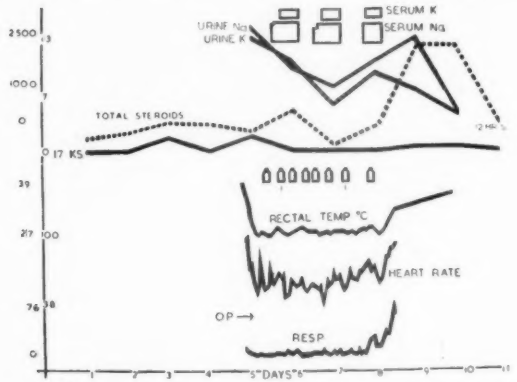

FIG. 5.—Chart summarising experiment on Dog 6. The excretion of total steroids and 17-ketosteroids is shown during the control period, during the period of hypothermia (27° C.) and during recovery. The "flasks" indicate bottles of 500 ml. of fluid. The "steroids" are measured in mg./twenty-four hours.

during the period of hypothermia, there is no adrenocortical response as evidenced by excretion of adrenocortical steroids, but as soon as the temperature is allowed to rise the response becomes evident. If this observation is correct, and it would seem to be so, it could be that by hypothermic anæsthesia we are preserving the adrenocortical responses to stress for the recovery period and not depleting the reserve of the patient during the operation.

CONCLUSION

It would be pleasant to be able to speak on one's subject with authority and unqualified enthusiasm. I would not dare to claim authority on the basis of a series of cases which is so small compared with those great series which have introduced or supported other anæsthetic procedures, nor can one claim authority on the grounds of our experimental work which is only at its very inception. Our enthusiasm is qualified by this lack of knowledge, but we know enough to appreciate that hypothermia is certainly no new anæsthetic technique with wide applications. We are, in fact, feeling our way, exploring new territory to discover whether it holds promise and new hope for the very sick and disabled. Let us regard hypothermia as a procedure which, like induced hypotension, can be utilized with benefit in exceptional circumstances and only in centres where there is the necessary special equipment, experienced personnel and, above all, adequate nursing facilities.

ACKNOWLEDGMENTS

I must express my very great gratitude to members of my Department and others associated with them who have permitted me to include their cases in this review, in particular to Dr. Jackson Rees, Dr. John Dundee and Mr. C. B. Sedzimir and other members of the Liverpool Neurosurgical Unit, and to Mr. John Shepherd for permission to quote the case of inguinal hernia. I am also grateful to Mr. Riddle, the physiologist in the Department of Anæsthesia, and to Mr. Ian MacPhee, Senior Lecturer in Surgery, for their help with the experimental work.

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Section of Obstetrics and Gynæcology

President—FREDERICK W. ROQUES, M.D., M.Chir., F.R.C.S.Eng., F.R.C.O.G.

[*April* 22, 1955]

DISCUSSION ON THE HAZARDS OF ANÆSTHESIA IN OBSTETRICS

[*Abstract*]

Mr. A. J. Wrigley: For some years I have felt that whereas enormous advances have been made in the nature and safety of anæsthetics and their administration in most other branches of medicine, what I may term "ordinary obstetric anæsthesia" has stood still.

The problem must be considered in two distinct categories—that of hospital and domiciliary obstetrics. About one-third of all babies born in this country are still born at home under the care of the family doctor and midwife. The former now receives little or no training in suitable anæsthetics to administer to women in labour and frequently this results in resort to the use of chloroform. Is this a good plan and can our anæsthetic colleagues suggest a safe and equally efficient method of anæsthesia for such patients?

In hospital too often the administration of anæsthetics to women in labour is left in the hands of the most junior member of the anæsthetic team. It is felt that this is not correct as so frequently these patients present a most difficult anæsthetic problem; they are tired, they have lost blood, and from an anæsthetic point of view are most inadequately prepared.

Therefore, a plea is made that a major problem exists which merits the serious and urgent consideration of the Faculty of Anæsthetists.

Dr. Derek Wylie: Some details of 31 anæsthetic deaths occurring in hospital and domiciliary obstetric practice are described. Particular attention is drawn to 15 of these, which were associated with vomiting or regurgitation. Death can be caused by acute anoxia or the results of aspiration into the lungs, but irreparable damage may be done to both mother and child even in cases where there is never any question of a fatal outcome. The frequency of vomiting with general anæsthesia in obstetrical cases is discussed, and five points are considered as a basis for tackling this problem: the use of local analgesia, the preparation of the patient, the anæsthetic, the posture of the patient, and the anæsthetist.

Although a wider use of local techniques would help to avoid the risk of anæsthetizing an unprepared patient, they cannot be the whole answer to the problem since there will always be occasions when a general anæsthetic is essential. It is not good medicine to starve or deprive of fluid for long periods a woman who is in labour, and the use of a stomach tube would therefore have to be routine to eliminate every chance of aspiration. This seems unjustifiable.

Special emphasis is laid on equipping the labour ward in the manner of an operating theatre, particularly in relation to the use of suction and an ability to posture the patient. A modified "Oxford" bed, which can be quickly tilted into either a head-down or a head-up position is described.

If all ancillaries are to hand there would seem to be no reason why an experienced anæsthetist should not successfully deal with the labour ward cases by methods he habitually uses for general surgery. The use of a cuffed endotracheal tube has much to recommend it.

Many obstetrical deaths due to anæsthesia can without doubt be prevented, and this is particularly true of those due to vomiting. The standard of labour ward anæsthetics should be brought up to that of the operating theatre, so that both mother and child can benefit from advances of the last decade. In the final event this will only be achieved by more experienced anæsthetists dealing with these problem cases.

Mr. John Peel: Has the obstetric patient benefited as much from the great progress in anæsthetic technique and knowledge as the surgical one? Maternal deaths due to anæsthesia have increased, proportionately if not absolutely. Anæsthesia plays a part in maternal morbidity because of pulmonary complications, and is also a cause of fœtal mortality and morbidity by reason of anoxia as well as the true action of the anæsthetic drug.

A rough estimate is that there are 50,000 forceps deliveries a year, and probably a fifth of these in the patient's own home, all requiring full surgical anæsthesia. Maternal deaths from anæsthesia occur both in domiciliary and hospital confinements.

Too many anæsthetics in hospital are given by juniors and in general practice by doctors inexperienced in anæsthesia. Not enough consideration is given by obstetricians and midwives to the preparation of the patient.

The following points are briefly mentioned as bearing upon safety of obstetric anæsthesia:

(1) The left lateral position for low forceps.

(2) Anæsthesia should be continuous once induced until the completion of the third stage.

(3) The more difficult obstetric operations following delayed labour are also the more hazardous from the anæsthetic viewpoint and require experienced personnel in both spheres.

(4) Special techniques such as caudal block have specific indications, but cannot be employed unless experienced anæsthetic personnel is available.

(5) The importance of blood pressure recordings in relation to anæsthetic risk is stressed.

(6) An adequate anæsthetic service for domiciliary midwifery is vitally important.

(7) Anæsthetic personnel is at least as important as anæsthetic agents.

(8) More anæsthetists, trained and interested in obstetric anæsthesia are needed, not only to administer anæsthetics, but to teach and to research into newer methods.

The following took part in the discussion: **Dr. E. H. Seward, Dr. R. B. Parker, Mr. O. Lloyd, Dr. D. A. Buxton Hopkin, Dr. O. P. Dinnick, Mr. G. H. Bancroft-Livingston, Mr. A. Walker, Dr. M. D. Nosworthy, Mr. E. D. Y. Grasby, Mr. J. V. O'Sullivan, Mr. G. F. Gibberd, Mr. W. Hawksworth, Mr. A. J. McNair.**

[*May* 13, 1955]

Spontaneous Uterine Rupture During Labour.—NORMAN MORRIS, M.D.

A specimen was shown of a uterus which ruptured spontaneously during labour. The patient, aged 25, had experienced 4 previous normal pregnancies and labours.

This, her fifth labour, was seemingly normal lasting just over two hours. The infant was born alive and the placenta delivered spontaneously. Shortly after this the patient became profoundly collapsed, although there was no associated post-partum hæmorrhage. A total hysterectomy was performed and she survived.

Careful scrutiny of this patient's previous history produced no evidence of any condition likely to predispose to the uterine rupture.

Rupture of the Uterus Occurring at the Time of Removal *per vaginam* of a Pedunculated Uterine Fibroid.—R. W. GRAYBURN, M.B., M.R.C.O.G.

The patient was a nullipara aged 52. Careful examination failed to reveal evidence of inversion of the uterus. The fibroid, as large as a golf ball, was removed easily by torsion and subsequently a ragged wound 1 in. in diameter was found in the uterine fundus. Hysterectomy was performed. It is thought that the "pedicle" of the fibroid was in fact a very localized and attenuated inversion of the uterus.

Rupture of a Pyosalpinx Associated with an Intra-uterine Pregnancy.—LYNN A. J. EVANS, F.R.C.S.

3 cases were described. The first presented a general peritonitis associated with a 14-week pregnancy. Recovery, complicated by a paralytic ileus, followed left salpingo-oophorectomy. The second patient had increasing lower abdominal pain with eight weeks' amenorrhœa. A large left pyosalpinx was excised. The corresponding ovary and appendages of the opposite sides were normal. Abortion occurred forty-four days and six days post-operatively respectively. The third died of peritonitis and septicæmia following rupture of a right pyosalpinx with a uterus didelphys, the left half containing a 24-week pregnancy.

Vaginal Metastasis of Hypernephroma.—N. GOURLAY, M.R.C.O.G.

A brief report of a patient whose only symptoms were related to a pedunculated vaginal tumour which was subsequently found to be a metastasis from a hypernephroma of the left kidney. Multiple pulmonary metastases precluded any treatment other than local removal of the tumour.

Carcinoma of the Cervix with Pulmonary Metastases.—C. A. SIMMONS, F.R.C.S., M.R.C.O.G.

Three X-ray films were shown of the chest of the patient, aged 55. She had been treated twenty months previously with a full Stockholm dose of radium, for a stage 1 anaplastic squamous cell carcinoma of the cervix. The patient remained free from secondary deposits from this time, until she was treated by her own doctor with penicillin for "bronchitis". Chest X-ray showed multiple "cannon ball" deposits. A further film four months later showed many of these to have disappeared, and a large one has regressed considerably without further treatment.

The patient remains quite fit.

Procidentia with Primary Carcinoma of the Vagina.—DAVID B. BROWN, M.B., M.R.C.O.G.

Multipara, aged 67. She had a prolapse of the uterus which had never been treated with a pessary, and had been irreducible for a year. The whole mass equalled the size of a fœtal head and the carcinoma extended to an inch from the os cervicis. The lesion was excised widely with high cervical amputation.

There was only one similar case in 120 primary vaginal neoplasms during the past forty-five years at the London Hospital.

Hydrosalpinx.—F. J. COCKERSOLE, M.B., M.R.C.O.G.

The specimen shown consisted of an unusually large hydrosalpinx measuring 7½ in. by 5¾ in. and weighing 1 lb. 12 oz. The pelvic inflammatory disease giving rise to the tumour occurred fifteen years prior to the symptoms of lower abdominal pain, and increasing abdominal enlargement, with which the patient presented. A large cystic abdomino-pelvic tumour was palpable, but was indistinguishable from an ovarian cyst until laparotomy was performed.

[*June* 24, 1955]

DISCUSSION ON CARCINOMA OF THE VULVA

THE following two papers by Mr. A. L. T. Easton and Dr. P. S. Andrews deal with some clinical and pathological aspects of the same material.

Mr. A. L. T. Easton:

The case histories of 143 histologically proven vulval cancers seen at the Middlesex Hospital and the Hospital for Women, Soho, in the past twenty-five years have been examined (Table I).

TABLE I.—CARCINOMA OF VULVA

	Cases
Total number examined	158
No histological report	15
Total	143

143 CASES

Epithelioma of vulva	119	83·2%
Rodent ulcer	9	6·3%
Melanoma	7	4·9%
Prepuce of clitoris	3	
Glans clitoris	1	
Sarcoma	1	
Bartholin's gland	2	
Adenocarcinoma. ? sweat gland	1	
	143	

During the same period there occurred at the Middlesex Hospital 1,863 carcinomas of the cervix, 896 carcinomas of the body of the uterus and 73 carcinomas of vagina. The corresponding figures from Soho are not available as far back as these, but 115 of the 143 cases were seen at the Middlesex during this period. This gives an incidence of 4% of all genital tract cancer being of the vulva (Table II).

TABLE II.—GENITAL TRACT CANCER
1930/1954
Middlesex Hospital

Cervix uteri	1,863	63%
Corpus uteri	896	30·5%
Vagina	73	2·5%
Vulva	115	4%
Total	2,947	

Age.—The average age for this condition was 62 years, when first seen, and Fig. 1 shows in a simpler form the relative age incidence in each decade.

The average age of the five-year survivals was 58 years. The oldest was 81 years and the youngest was a girl of 15½ years. She was treated just under three years ago by radical vulvectomy with external iliac lymph node dissection in the manner described by Taussig, without sacrifice of the inguinal ligament. She is alive and well to-day without recurrence.

The superficial nodes were involved but not the deep group.

Symptoms.—Fig. 2 illustrates the predominant symptoms expressed diagrammatically according to their relative frequency. The patient most frequently notices the lesion itself.

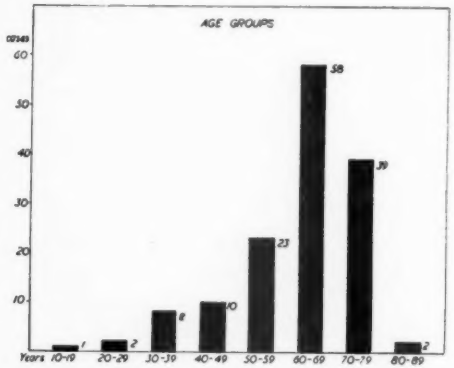

FIG. 1.—Carcinoma of vulva: 143 cases.

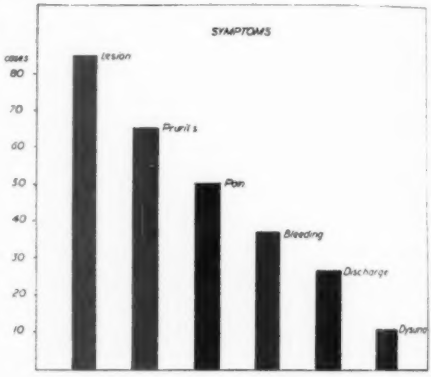

FIG. 2.—Carcinoma of vulva: 143 cases.

Presence of Another Carcinoma

Of the 143 cases, in 6 of them (i.e. 4·2%) the patient already had or later developed a second cancer.

Attention is drawn to the number of rodent ulcers, viz. 9 (or 6%). The single case of carcinoma of the glans clitoris is also of interest. Most cases of carcinoma of the clitoris are preputial and here 3 occurred.

Those clitoral cancers arising from the prepuce or the neighbouring skin and which involve the clitoris secondarily, behaved as other epitheliomata of the vulva, and spread via the lymphatic channels. These are therefore included in the 111 vulval epitheliomata (Table III). The one from the glans itself pursued an almost volcanic course. In the space of six

TABLE III.—CASES FOLLOWED FOR OVER THREE YEARS

127 *divided as follows*

Epithelioma of vulva	111
Rodent ulcer	8
Melanoma	5
Glans clitoris	1
Sarcoma	1
Adenocarcinoma of Bartholin's gland	1
	127

TABLE IV.—DEATHS FROM INTERCURRENT DISEASE

Senility	3
Heart failure	1
Lung abscess	2
Carcinoma elsewhere	6
Suicide—barbiturate	1
Pulmonary embolus	1
Cerebral thrombosis	1
Coronary thrombosis	1
Diabetes mellitus	1
	17

weeks it had spread via the blood stream to the ovary, liver, brain and lungs. This patient died within two months of the diagnosis being made. Only palliation by simple excision was possible.

For the purposes of assessing survival, all cases seen later than June 1952 have been excluded. Thus a three-year survival is taken as the minimum.

There were 127 cases in this group of which 124 were epitheliomata. One adenocarcinoma of Bartholin's gland, the sarcoma and the carcinoma of glans clitoris are not included.

Leukoplakia.—Inadequate recording and diathermy destruction of biopsy material precluded an estimate of the incidence of this factor.

Deaths from Intercurrent Disease

These numbered 17 (Table IV). All took place a considerable time after leaving hospital.

Size of Tumour

In 84 cases the size of the tumour was recorded and these have been grouped arbitrarily as small, medium and large:

Small tumours being those whose diameter was less than 2·5 cm., medium being those up to 5 cm. diameter and anything over 5 cm. was classified as large. On this basis:

43 cases had small tumours.
26 „ „ medium-sized tumours.
15 „ „ large tumours.

No unexpected relationship between the size of the tumour and the survival rates was found. The larger tumours on the whole doing worse and the medium-sized ones best.

Length of History

104 cases gave a history of one year or under and of these 36 lived longer than five years. 20 had symptoms for over a year and of these 10 lived over five years.

Treatment

I have, for the purposes of comparison, taken under the heading simple vulvectomy and local excision all cases where any operation that did not include lymph-node dissection was done.

Radical vulvectomy with superficial node dissection comprises the other main group. This operation was the one practised by the late Mr. Victor Bonney and many of these cases were performed by him. The so-called node of Cloquet was not therefore removed.

A small number had radiotherapy as a primary treatment with local diathermy to the tumour. Only 12 cases were so treated, 6 of whom survived three years, 5 for five years, and 1 for ten years.

The last and more recent group of all is of those having a radical vulvectomy with both inguinal and iliac node dissection. These cases were too few and too recent to be of any significance. 11 cases altogether have been done, 8 of which were more than three years ago. Of these 4 are dead. One of the recent ones had had a recurrence with deep femoral thrombosis.

In analysing the results of treatment, I have taken the three-, five- and ten-year survival (Table V).

TABLE V.—CARCINOMA OF VULVA. 124 CASES
Absolute 3-, 5- *and* 10-*year survival*

	3-year	5-year	10-year
All cases 124..	53%	47%	32%
Cases treated 119..	55%	49%	34%
PRIMARY TREATMENT			
Vulvectomy and local excision 43	67%	61%	36%
Radical vulvectomy superficial dissection 46	54%	49%	45%

TABLE VI.—CARCINOMA OF VULVA: 124 CASES
Relative 3-, 5- and 10-*year survival*

	3-year	5-year	10-year
All cases 124..	55%	49%	34%
Cases treated 119..	58%	50%	36%
Vulvectomy and local excision	70%	65%	46%
Radical vulvectomy superficial dissection	56%	51%	48%

5 cases were not treated, 4 were considered inoperable because the growth was too advanced. One refused treatment and all died within one year. The operability rate was 96%. The absolute survival is expressed as a proportion of those originally presenting and the relative survival is arrived at by deducting those dying of intercurrent disease from the original group (Table VI).

Operative mortality

Some 49 simple vulvectomies or local excisions were performed with one immediate death from post-operative embolus. 43 of these were as a primary treatment and the embolus occurred in one of these.

59 cases were subjected to radical vulvectomy with inguinal node removal, 46 of these being as primary treatment. None died from the operation or its immediate consequences.

11 cases have had a radical vulvectomy with iliac node dissection as primary treatment without a death. The operative mortality for the whole series is therefore less than 1%.

Half the total rodent ulcers and half the Bowen's disease and other pre-invasive carcinoma of skin fell into Group I. A significantly large number of Grade I tumours were also found to have been treated by simple vulvectomy or local excision.

The fact that no node removal was undertaken in the cases undergoing simple vulvectomy seems to us to reinforce the significance of these figures, since a few without clinical evidence of node involvement will have had deposits present at the time of operation. It is probable many were selected for this treatment because of the absence of palpable nodes. Indeed, according to calculations based on the figures obtained from the cases undergoing node removal, between 10 and 15% of the simple vulvectomy group will have had deposits in the nodes.

Tables V and VI show the results of treatment in the whole series and in that of the two largest groups.

Because of the unexpectedly good results of simple vulvectomy it was decided that where possible the original and subsequent sections of the tumour should be examined. This was possible in 115 cases, of which 114 were composed of squamous epithelioma, rodent ulcer and Bowen's disease or atypical proliferation. The tumours were graded by Dr. P. S. Andrews into three classes, according to the histological degree of malignancy and the results correlated with the subsequent fate of the patient. It became apparent from this investigation that the surprisingly good results of treatment in the simple vulvectomy group were certainly due to the inclusion of a high proportion of the less malignant cases.

It has already been conclusively shown that lymph-node involvement at the time of operation renders the prognosis extremely grave, but it is not clear whether any differences in prognosis can be given according to whether the superficial inguinal group alone or the iliac group of nodes is involved. Some authors in the past (Smith and Pollack, 1947), while allowing that an extended dissection is theoretically more likely to produce improved results, question in fact whether any real gain is achieved having in mind the outlook for those where the superficial nodes only are involved by tumour, and secondly the very considerable increase in the severity of the operation and its attendant high primary mortality and morbidity, particularly in elderly women.

In conclusion we feel that the likelihood of the superficial inguinal nodes being involved is greatest in the tumours of histologically high-grade malignancy and lowest in those of low-grade malignancy. If this is true then it would be logical to suggest that in those cases with low-grade tumour and on whom superficial inguinal node removal is done, as it must be, then, if they are free from invasion a radical iliac dissection would not be indicated. This would apply particularly to the elderly and more frail patient.

It is in the middle-grade group that the difference in technique is likely to prove critical. For here the prognosis is less predictable and in the fit patient a strong case for iliac node clearance can be made.

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Dr. P. S. Andrews:

Carcinoma of the vulva is a relatively rare disease. As with squamous carcinoma elsewhere there are wide variations in the differentiation of the tumours; these are reflected in their clinical behaviour. By studying a large enough series of vulval cancers one can get an idea of their range of histological malignancy and correlate it with their clinical behaviour. We have collected all cases from the Middlesex Hospital and the Hospital for Women, Soho Square, from 1930 onwards. These amounted to 114 cases. They were divided into three grades of malignancy, assessed histologically, the criteria being keratin formation, cell size and mitotic figures. These criteria are comparable with those of Broders (1926); he divided his cases into four grades; we have used only three (Figs. 1, 2 and 3):

There were difficulties in grading some squamous carcinomas, particularly when the tissues sectioned had been obtained during diathermy coagulation (Fig. 4).

Whilst attention was directed towards squamous cell carcinoma we nevertheless examined tissue from all cases with a diagnosis of malignant disease of the vulva. This included basal cell carcinoma or rodent ulcer, malignant melanoma, Bartholin's gland carcinoma and fibrosarcoma. These last three—malignant melanoma, Bartholin's gland cancer and fibrosarcoma—will not be discussed further.

There were also 9 cases diagnosed clinically and treated as carcinoma. Microscopy of the lesions showed no evidence of invasion of the dermis. 3 were identical with Bowen's disease and the remaining 6 were labelled atypical epithelial proliferation without invasion. In view of this absence of invasion and the tendency for intra-epithelial malignancy to follow a less dangerous clinical course, these cases were separated from the squamous cell cancers. Further sections from paraffin blocks of tissue did not show invasion.

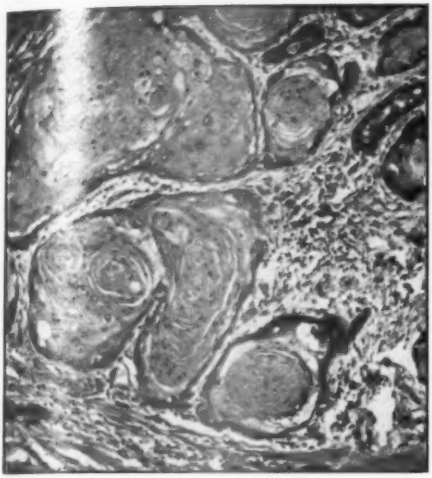

FIG. 1.—Grade 1—or well differentiated—squamous cell carcinoma with plentiful keratin formation and even cell size. × 75.

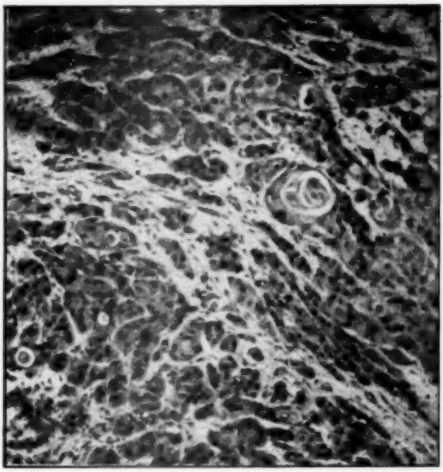

FIG. 2.—Grade 2—or averagely differentiated—tumour. There is less keratin formation, the cells vary in size and mitoses are present. × 75.

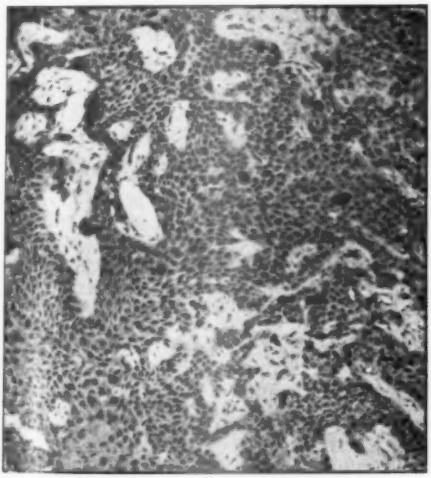

FIG. 3.—Grade 3—or poorly differentiated—tumour. There is very scanty keratin formation; the cells are irregular and mitoses are numerous. × 75.

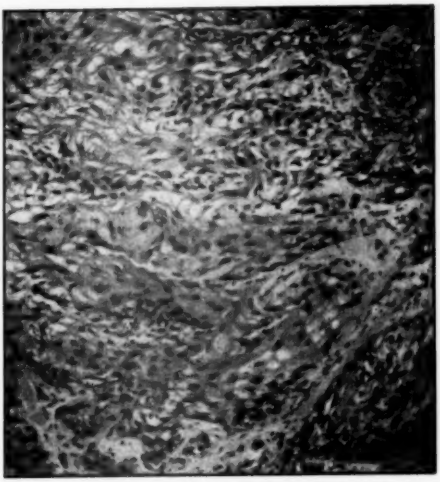

FIG. 4.—The immediate effect of diathermy on a squamous cell carcinoma. There is so much distortion that the tumour could not be graded. × 75.

Type of Tumour

The distribution of tumours is shown in Table I. There were more tumours classified as Grade 2 than any other grade. Furthermore there were more well differentiated (Grade 1) than poorly differentiated tumours (Grade 3).

Perhaps it is unusual to meet as many rodent ulcers as we did; they amount to 8% of the series. There is no doubt that they may be mistaken histologically for undifferentiated, non-keratinizing squamous cell cancers but their clinical course is quite different, they grow slowly and hardly ever metastasize.

Rodent ulcers were separated from the squamous cell cancers and dealt with on their own, likewise Bowen's disease and other intra-epidermal atypical proliferations.

TABLE I.—DISTRIBUTION OF THE TUMOURS SEEN IN THE LAST 25 YEARS

Squamous cell carcinoma Grade 1 ..	36
Squamous cell carcinoma Grade 2 ..	46
Squamous cell carcinoma Grade 3 ..	14
Bowen's disease and other atypical epithelial proliferations	9
Rodent ulcer	9
Total	114

Lymph-gland Involvement

There were 75 cases of squamous cell carcinoma treated more than 5 years ago in which the follow-up data were complete.

Comparing the incidence of lymph-node invasion at the time of operation—the left-hand columns from each grade—there was a higher incidence with the less differentiated tumours. Thus 10/31 of Grade 1 tumours showed invaded glands, 19/32 of Grade 2 and 8/12 of Grade 3 tumours (Fig. 5).

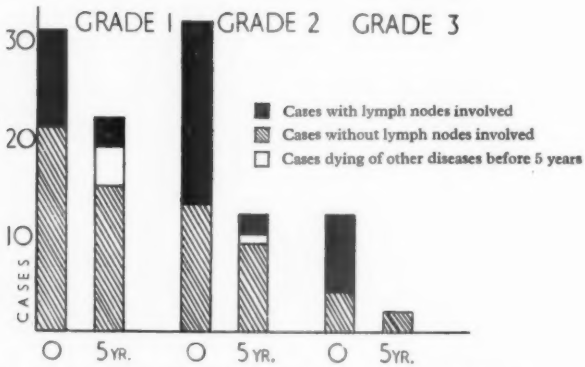

FIG. 5.—Showing the relationship between grading, lymph-gland involvement and five-year survival.

The overall rate of lymph-gland involvement on clinical or histological grounds was 50%. We have seen that Grade 1 cases show a much lower rate, therefore it seems reasonable to argue that any series of cases with a low incidence of node involvement would contain a greater proportion of Grade 1 tumours than this series. Conversely an overall rate exceeding 50% would be due to a greater proportion of higher-grade tumours in the series.

Results

The prognosis is related to the grading; there are fewer survivors amongst patients with the higher-grade tumours. Most cases dying within five years showed lymph-node invasion at the time of operation.

There is a slightly more favourable five-year survival amongst patients showing node involvement in Grade 1 than in Grade 2. The figures are small and therefore the proportion of 30 : 10% must be regarded only as a tendency and not on its face value.

The Grade 1 node-free survival rate as a percentage is 75; discounting the 4 who died of intercurrent disease it becomes 95%.

Simple vulvectomy was performed mostly on cases without clinical evidence of node involvement having Grade 1 or Grade 2 tumours. These have a better five-year survival than others (Fig. 5) and therefore the good results of the treatment were due probably to the grade of tumours.

We cannot, at the moment, compare the results of vulvectomy and inguinal node excision with the vulvectomy and inguinal plus iliac node excision; our numbers of cases being too few. It will be interesting to see which method of treatment offers the best chance for a patient with glandular metastases. These are about 50% of all cases and present a difficult problem.

There was no association between grade of tumour and the patient's age.

Rodent ulcers did well, 6 out of 8 survived five years, the 2 who succumbed had incompletely excised lesions and died with active rodent ulcers.

Bowen's disease and other intra-epidermal atypical proliferations also did well, 5 out of 8 were alive and well after five years. One case died of cancer. This case was reviewed and it was found that the biopsy showed Bowen's disease only, yet the patient had an ulcer which was not included in the biopsy. It is well known that Bowen's disease eventually breaks its bounds and becomes actively invasive. It seems likely that this had occurred in this case. The other 2 deaths were from intercurrent disease; there was no evidence of recurrence at the time of death. The remaining 5 are alive, 2 had further treatment for local recurrence of Bowen's disease.

Thus rodent ulcers, Bowen's disease and other pre-invasive lesions carry better prognosis than squamous carcinoma. It is best to separate them from squamous cancer when comparing the results of treatment.

Local Recurrences

25 patients have, so far, developed vulval recurrences of squamous cell carcinoma. The interval between treating the primary and the appearance of a recurrence varied from one to twenty years, whilst half of the recurrences occurred within five years.

The histological sections of some smaller recurrences showed that squamous carcinomas had arisen in areas of leukoplakia. The slides of all primary carcinomas were then re-examined and in 77 sections there was a sufficient margin of skin to ascertain the presence or absence of leukoplakia around the primary tumour. The results were correlated with the subsequent development of local recurrences as shown in Table II,

TABLE II.—HISTOLOGICAL INCIDENCE OF LEUKOPLAKIA

Leuko-plakia	Total	Cases with "recurrence"	Cases without "recurrence"
Present	50	19	31
Absent	27	4	23

from which it appears that the chances of recurrence are greater when leukoplakia is present around the primary cancer. Therefore a wide excision of all leukoplakia-bearing skin with the primrry tumour should reduce the incidence of local recurrences.

SUMMARY

75 cases of squamous cell carcinoma of the vulva have been reviewed, and the histological material graded according to their differentiation.

There are differences in the five-year survival rate between the grades.

It is suggested that to compare the results of treatment without knowing the distribution of tumours in the grades leads to unnecessary confusion.

Part of the expenses of this investigation were defrayed by the British Empire Cancer Campaign.

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Mr. Stanley Way: The treatment of carcinoma of the vulva is by surgery. The operability rate is high (83%) and the absolute survival rate is high (61%). When the lymph nodes are not involved the survival rate is very high (86%), and when the lymph nodes are involved—as is common in any cancer—the survival rate is much lower (48%) but it is still high enough to make surgery a rewarding line of treatment (Way, 1954).

The common co-existence with carcinoma of pre-malignant lesions in other parts of the vulva necessitates a wide excision of the vulva if new primaries are to be avoided, and this is also a strong point against the treatment of this disease with radium.

The Operation

The operative technique that I introduced differed from those previously described in two respects. Firstly, the removal of the vulva is very extensive, and, secondly, the node dissection is much wider. Although it soon became apparent that this operation was giving better results than those tried before, it was some time before it could be seen which of these two points was responsible for the better results—the wide removal of the vulva, the extensive node dissection or, perhaps, both. It seems now that the wide vulval removal is the most important step in the operation.

Nodal Involvement

In the series that have passed the five-year mark there have been no local recurrences. Out of 143 cases which we have fully studied we have found deep node involvement in only 5% of the total cases although 43% of all these cases had nodes involved. Thus only

15% of our patients could have benefited by the deep node dissection even if they had all survived. In actual fact, out of 9 cases with deep node involvement 2 survived five years: 1 is alive and well twelve years after operation and the other after eight years. Following the introduction in 1952 of the rapid node-smear method of assessing node involvement (Dearing, 1952) I have adopted a new approach. I now explore the iliac vessels by an incision through the external oblique and remove any palpable node. If none is palpable then the lowest lateral and medial external iliac nodes are removed. The removed nodes are smeared and, if negative, no further deep dissection is carried out and the inguinal ligament is not divided. If positive, the operation proceeds as before. It is as yet too soon to assess fully the results of this procedure but so far they do not seem inferior to those previously obtained.

It is vitally necessary in my opinion to remove the superficial nodes since they are too widespread and numerous to lend themselves to the node-smear technique. Further, our experience has shown that no less than 43% of nodes which *cannot* be palpated clinically contain cancer when they are sectioned.

We have classified our tumours from the histological standpoint according to the method of Glucksmann (1945) and have divided them into anaplastic and differentiating. The anaplastic tumours have significantly greater incidence of node involvement than the differentiating tumours and when the nodes are involved they are more widespread in anaplastic variety of cancer.

We have seen at least one type of tumour where the histological pattern of the biopsy gives some idea of the possible outcome. This tumour is characterized by large round basal type cells with little or no stroma and with a tendency to form malignant giant cells. We have seen five examples of this. All gave short histories, all had large tumours and widespread node involvement and treatment failed in every case.

For a long time it was our practice to leave the vulval wounds open and allow them to granulate. This process has many disadvantages and very recently we have experimented with plastic closure of the vulva. Of the methods that we have tried the "split thigh flap" method has given the best results. The incision into the thigh over the saphenous vein which I described previously (Way, 1948) is extended downwards. It will then be found that the medial side of this flap can be undercut and brought across to the mid-line to close the vulval wound, whilst the lateral part of it can be elevated to cover the femoral vessels. By this means complete closure of a very wide excision can be obtained and, so far, out of 6 cases we have secured primary healing in 5. The post-operative period is very much smoother than by the old method and we believe that this will reduce the operative mortality.

Late Results

The late results of the operation have been encouraging. Subsequent to the fifth year after operation five "recurrences" or fresh primaries have occurred out of 53 patients. 2 have been successfully re-treated and are living and well. 3 have died. Our patients have not had to lead a life of invalidism and even when the entire area has been left to granulate the scars have tended to become almost unnoticeable by the third year.

5 of our patients have become pregnant after operation, 2 of them twice and 1 has had a normal delivery. The remaining 4 have been delivered by Cæsarean section.

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Mr. Anthony Charles: Radical vulvectomy as performed to-day usually leaves a large area of tissue surrounding the vaginal and urethral orifices denuded of skin. Now early skin cover is one of the first principles of wound surgery, and radical vulvectomy certainly produces a grievous wound. When this wound has healed by granulation and epithelialization, the vulval area on occasions is a very distorted possession for any woman. It would perhaps be feasible to cover the area with free skin grafts, applied at the time of the vulvectomy. It is no good asking the plastic surgeon to cover the area several days later when it is exuding pus. I solicited the help of Mr. H. Elliott Blake, plastic surgeon at St. George's Hospital, in devising flaps from the thigh to cover over the vulva, and the deposition of these flaps is Mr. Blake's work. It will be seen from Figs. 1 and 2, illustrating the incisions, that the flaps which cover over the raw area at the vulva are derived from the thigh, and therefore depend for their blood supply upon vessels running in an upward direction—not the most favourable. In cutting these flaps it is essential that the base attached to the thigh is broader than the top. The thigh flaps (T) are transposed in a sideways and semi-rotary

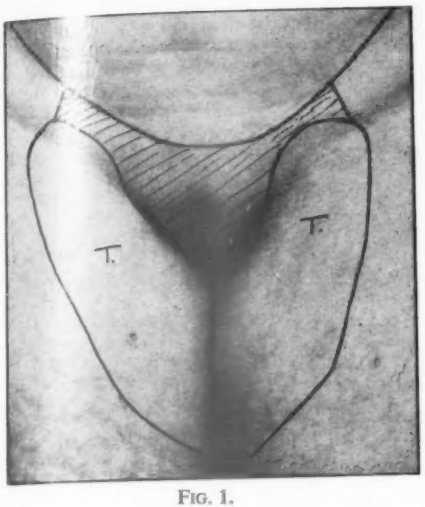

FIG. 1.

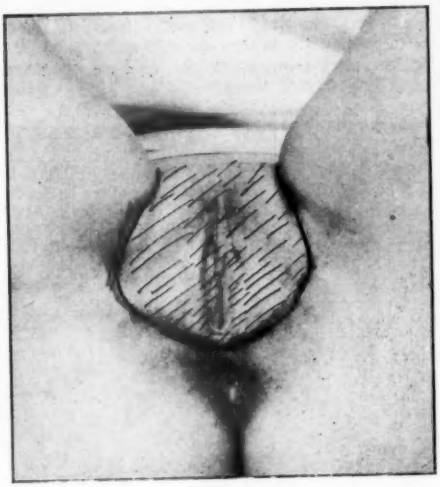

FIG. 2.

FIGS. 1 and 2.—Incisions for vulvectomy. Shaded area is tissue removed.

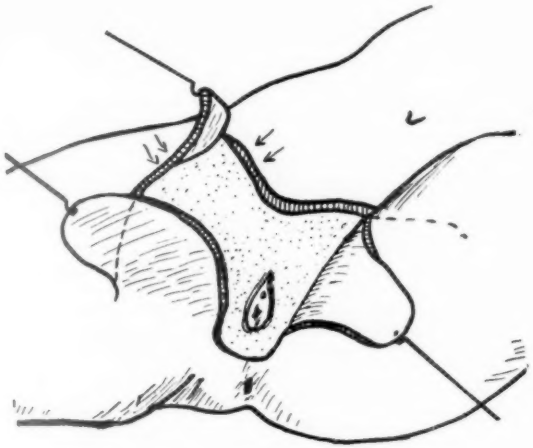

FIG. 3.—Vulva excised and flaps raised.

direction. To cover the bare area around the vagina, their medial edges are sutured to the vaginal mucosa below and to each other above. Fig. 3 attempts to show the movement of the flap, but it is rather difficult to draw in one plane a manœuvre which takes place in two different planes. The skin is mobilized all round by undercutting the large abdominal flap and the lateral borders of the incisions in the thigh. By adequate mobilization it has been possible to close the wound completely after transposing the thigh flap.

In 5 of the 6 cases I have treated by this method, the transposition of the thigh flap was carried out at the same time as the vulvectomy, without any prior preparation. They all did reasonably well, in fact, in every case there was primary healing round the vulva, but there was some sloughing at the top of the flap in the groin. The most favourable case is a plump multipara, and the worst result was obtained in a comparatively thin nulliparous woman. In that case I had to do partial secondary suture. The last case which we did was by a different technique, inasmuch as the thigh flap was raised and undercut for about 1½ in. all round the edges, and then lightly sutured back in place and left for ten days or so.

By this manœuvre the blood supply to the flap is cut off round the sides and top, and in ten days time it has derived a greatly increased blood supply from its base. Then the operation was carried out as before, excising the scar round the flap. This resulted in clean healing except for one small area about 2 in. long and ½in. wide on the right-hand side (Figs. 4 and 5).

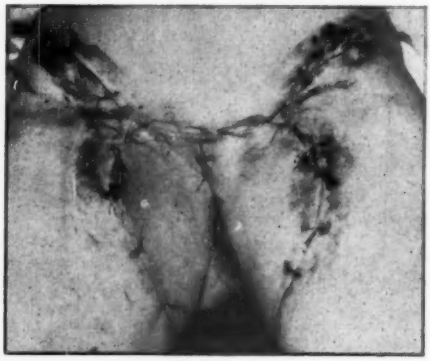

FIG. 4.

FIG. 5.

FIGS. 4 and 5.—Patient treated by "delayed flap" method ten days after operation.

The time spent in hospital for these two operations was about five or six weeks, which may not be much less than the stay in hospital when the vulva is left to granulate, but I submit that the end result is far superior.

Operative Technique

For vulvectomy I have divided Poupart's ligament in each case, and dissected glands as far as the bifurcation of the common iliac artery. In no case have any of these glands been invaded by growth, so that the extent of the operation is probably in excess of what is necessary for cure in most cases. I have carefully united the divided ends of Poupart's ligament, and have sewn the medial portion to the pectineus fascia, so as to close the femoral canal as far as possible after the removal of Cloquet's gland. This closure must not be done too assiduously, or partial occlusion of the femoral vein may result. Drains are inserted in both groins, and at the symphysis pubis, and the dressings are firmly applied. So far none of these cases has developed a hernia, and there has not been any recurrence.

While I suggest that a formal operation of this type is not applicable to the large growths that have been shown by Mr. Way, it is, I feel sure, an adequate excision for the smaller growths of the vulva, which represent the bulk of the cases we see in Southern England. It is unnecessary to leave a large granulating wound after removal of a growth of moderate size, and primary skin cover brings considerable benefit to the patient.

Section of Pædiatrics

President—G. H. MACNAB, M.B., F.R.C.S.

[*June* 25, 1955]

MEETING AT THE GENERAL INFIRMARY, LEEDS

Diagnostic Swabs in Pertussis.—ANDREW BOGDAN, M.D.

"Whooping-cough has now achieved the notoriety of being more deadly to infants than any of the common infectious diseases. This is because the patient is highly infectious well before the nature of the illness can be diagnosed" (Ministry of Health, 1954).

Swabs from pertussis contacts support this statement. However, their results provide evidence that pertussis can be diagnosed in the symptom-free incubation period up to four days before the first cough or catarrhal symptom appears (Bogdan, 1951*b*).

Indication for swab diagnosis.—The obvious use of swabs is in symptom-free contacts or children in the early pre-paroxysmal stage, when isolation may limit spread of infection and suppressive treatment modify the disease (Bogdan, 1951*a*, *b*, 1952). A recent editorial (*Brit. med. J.*, 1953) suggested that "the most rational use of antibiotics is in the treatment of contacts before they develop the typical symptoms of the disease". The suitability of suppressive treatment in institutions has been pointed out (*Lancet*, 1951). Atypical cases following immunization and parapertussis can only be diagnosed by swabs. Tempered by clinical judgment, it may be possible to exclude infectivity in contacts and in clinical cases after an antibiotic has been used; to curtail quarantine is a matter of some social significance. Therapeutic trials, such as the Medical Research Council's Pertussis Vaccine Trial (1951) and Antibiotic Trial (1953), are dependent on swab diagnosis. Good results may encourage the wider use of swabs and epidemiological research in pertussis.

Clinical assessment of swab accuracy.—This depends on each patient being a "known" case of pertussis by ascertaining exposure to infection, duration, nature and progress of symptoms, hence appreciation of the precise stage of the illness when swabs are taken; also if immunization may have modified the disease. If an antibiotic has already been used or there is a history of previous pertussis, then swabs would be negative. Swabs should be taken in the pre-paroxysmal stage and certainly no later than the 10th day of the paroxysmal stage when infectivity is waning (Kristensen, 1933). Such swabs may be expected to yield a positive culture and so individual accuracy can be assessed; especially if cultured within three to five hours on a highly selective medium, such as diamidine-fluoride-penicillin medium on which my swabs were cultured. Lacey's figures (1954) show that this medium yielded between 15 and 30% more positive cultures than Bordet-Gengou-penicillin medium on absolute diagnostic reckoning. Nicholson's and Turner's (1954) highly selective medium is also suitable for parapertussis.

Results.—The measures, preliminary to clinical assessment of swabs outlined above, were observed in my study of swab technique thus reducing the problem of accuracy in diagnosis to one of reliability in swab contamination. With cough such a constant feature of pertussis, it seemed reasonable to utilize cough to contaminate swabs.

The first of the two new techniques utilizing cough contamination of swabs was the supralaryngeal. The latter was described to this Section when initial results appeared promising (Bogdan, 1951*c*). The second was a pernasal technique modified for use with supralaryngeal swabs. Bradford and Slavin (1940) had initially used pernasal swabs for taking nasopharyngeal cultures in pertussis. In the supralaryngeal technique I aimed to get obvious contamination of the swab with laryngeal mucus brought up by cough; the same principle applied in the modified pernasal technique. Both new techniques have been fully described recently.

With practice and exercising care to acquire a portion of freshly expectorated mucus from the larynx, the average swab accuracy of each supralaryngeal swab rose to 92·5% (37/40) in "known" cases.

The combination of a supralaryngeal swab with my modified pernasal technique resulted in bacteriological confirmation of the diagnosis in 84% (92/109) of "known" cases. This combined technique offers the bacteriologist the best material for a positive culture, and is especially useful if for any reason the physician taking a single supralaryngeal swab fails to get visible, hence satisfactory, contamination of his swab.

The application of these new techniques may further the ultimate control of pertussis by assisting to solve the problem of early diagnosis stressed in the Report for 1953 by the Chief Medical Officer of the Ministry of Health.

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The Significance of *Hæmophilus Influenzæ* in Bronchiectasis of Children.—E. C. ALLIBONE, M.D., P. R. ALLISON, F.R.C.S., and K. ZINNEMANN, M.D.

In 32 children with chronic purulent bronchiectasis, observed for five to thirty-six months, non-capsulated *H. influenzæ* was the predominant organism in the sputum and was present in antrum washings in 19 (59·4%). Appropriate chemotherapy reduced the amount of sputum and eliminated pus and *H. influenzæ* simultaneously. During prolonged treatment a total of 204 relapses occurred of which 51% were due to *H. influenzæ*, 9·3% to other bacteria; in 39·2% no bacterial agent could be recognized. *H. influenzæ* is regarded as the organism responsible for the inflammatory process in chronic purulent bronchiectasis.

A full account will be published elsewhere.

The Antibiotics in Bacillary Dysentery.—E. F. MURPHY, M.D., M.R.C.P.Ed., D.C.H.

Bacillary dysentery has become widespread in the community. It is now frequent in epidemic form in children's hospitals and institutions throughout the country. Table I shows the notifications to the Registrar-General since 1940.

TABLE I.—NO. OF CASES NOTIFIED EXCLUDING ORIGINAL NOTIFICATION IN PORT HEALTH DISTRICTS

Year	No.	Year	No.	Year	No.
1940 ..	2,845	1945 ..	16,247	1950 ..	17,271
1941 ..	7,292	1946 ..	7,870	1951 ..	28,564
1942 ..	7,077	1947 ..	3,761	1952 ..	14,520
1943 ..	7,877	1948 ..	5,084	1953 ..	18,409
1944 ..	13,000	1949 ..	4,519	1954 ..	31,834

Effective treatment in the form of the wide-spectrum antibiotics is now available. The results of this application to a series of 500 cases admitted to Seacroft Hospital, Leeds, from January 1952 to May 1955 are shown in Table II. 26 cases were excluded because of doubt in the bacteriology. Of the 474 remaining, 62 were treated with sulphonamide and the remainder with Aureomycin or Terramycin/streptomycin in combination. Three consecutive negative stools after treatment constituted a success, a single positive constituted a failure.

TABLE II.—RESULTS OF TREATMENT WITH COMBINED TERRAMYCIN/STREPTOMYCIN, AUREOMYCIN ALONE AND SULPHONAMIDE ALONE

	Terramycin/streptomycin combination				Aureomycin				Phthalylsulphathiazole				Total
	Sonne		Flexner		Sonne		Flexner		Sonne		Flexner		
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	
Success..	154	98·72	97	91·51	22	95·65	118	92·91	41	68·33	2	—	434
Failure..	2	1·28	9	8·49	1	4·35	9	7·09	19	31·67	0	—	40
Total ..	156		106		23		127		60		2		474

The scale of dosage is shown in Table III.

TABLE III.—SCALE OF DOSAGE—SIX-HOURLY

Age	Aureomycin	Terramycin and streptomycin	Phthalylsulphathiazole
Under one year	100 mg.	100 mg. a.a.	0·5 gram
Under five years	150 mg.	150 mg. a.a.	1·0 gram
Over five years	250 mg.	250 mg. a.a.	2·0 grams

Duration of treatment.—Seven days' therapy was given in this series. But it was felt that five or even four days' antibiotic therapy might be sufficient.

Duration of stay in hospital.—25·3 days was the average figure for this series. Many patients were delayed because of other pathogens found in the stool and actually a period of sixteen days in hospital is sufficient with this antibiotic therapy to rid the patient of the organism.

Results.—It is clear that both Aureomycin and Terramycin/streptomycin in combination are highly effective in the treatment of both Sonne and Flexner dysentery. Ill patients responded immediately. Little supportive therapy was required, only a few cases requiring parenteral fluids. In the Flexner group one death occurred—an infant of seven weeks who showed septicæmic features, developing peripheral gangrene. Aureomycin failed to control the illness.

Discussion.—In other Sections of this Society the abuse of antibiotics has been discussed. Dangers resulting from superimposed infections are now well known. Accounts of fatal staphylococcal diarrhœa have appeared in the literature (Williams, 1954).

Staphylococcal superinfection occurred to a small extent in this series. One patient developed a bloodstained diarrhœa with colicky abdominal pain at the close of his treatment with Terramycin/streptomycin. He showed considerable toxæmia but responded quickly to erythromycin. 9 cases of acute staphylococcal pharyngitis occurred, presenting as sore throats with punctate injection of the palate. 4 of these required erythromycin therapy. A number of other patients in the series showed minor skin sepsis from which resistant strains of *Staphylococcus aureus* were isolated.

In conclusion it must be said that while the antibiotic therapy of bacillary dysentery is highly effective in curing the patient and in clearing the infection it carries the potential danger of invasive disease by other organisms. The prevention of this complication requires close supervision and may require the early cessation of treatment and, if needs be, the substitution of an antibiotic to which the invasive organism is sensitive. Bacteriological control is essential and adequate isolation of the patient important. When these safeguards are adopted the dangers of superinfection become less serious, so that it is felt that the treatment is entirely justified in hospital practice.

My thanks are due to Dr. E. C. Benn, Consultant Physician, Seacroft Hospital for permission to discuss this series of cases and also to Dr. H. E. de C. Woodcock who planned the treatment of these patients. The bacteriology was carried out by Drs. W. I. Johnston, G. M. Williamson and K. Zinnemann at the Department of Bacteriology, Leeds University Medical School.

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Observations upon Serum-penicillin Levels Following the Intramuscular Administration of Penidural.—R. J. PUGH, M.R.C.P., and K. ZINNEMANN, M.D.

The prolonged action of benzathene penicillin (Penidural) injected intramuscularly may prove of value in preventing streptococcal infections in rheumatic subjects. We have carried out serial serum-penicillin assays on children so treated to find how long protective levels are maintained, and have also studied the bacteriology of the children's throats during such treatment.

Method.—The administration of Penidural was related to body-weight. 17 children were given a single intramuscular injection of 10,000 units Penidural per pound body-weight. 20 children received weekly injections of Penidural; 13 of these 20 children were given 10,000 units, and the remaining 7 15,000 units per pound body-weight per week. The children were all bled twice weekly and the serum-penicillin levels determined. Throat swabs were taken at the same time as the bleedings.

Results.—Clinical: Administration raised no difficulties, but unless the proper procedure of slow deep injection was carefully observed pain was immediately felt. Only the upper, outer quadrants of the buttocks were used for injection sites. Subsequent local tenderness was constant, prompting caution whilst sitting during the day following injection. The

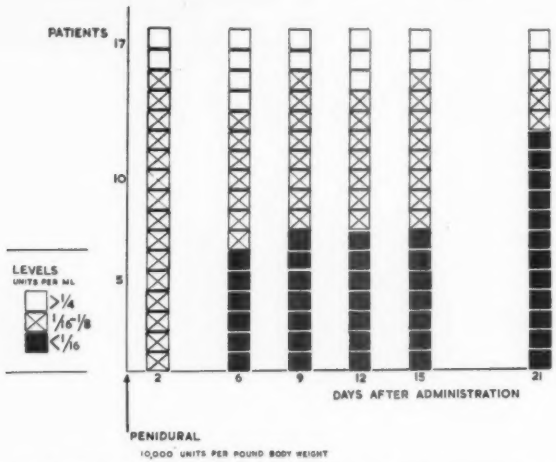

FIG. 1.—Penicillin blood levels in 17 patients after a single injection of Penidural.

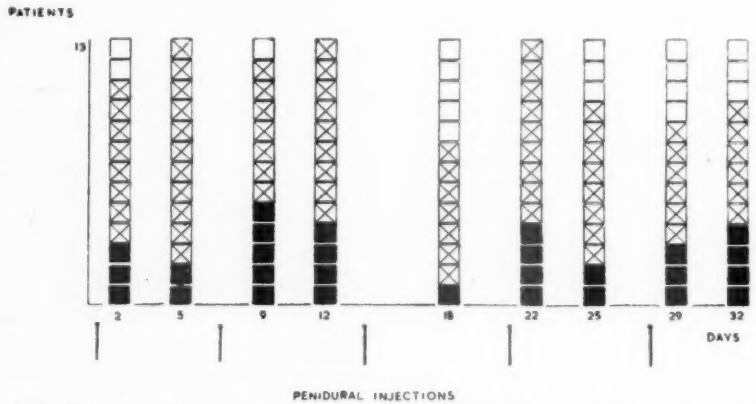

FIG. 2.—Penicillin blood levels in 13 patients receiving Penidural by weekly injections of 10,000 units per pound body-weight.

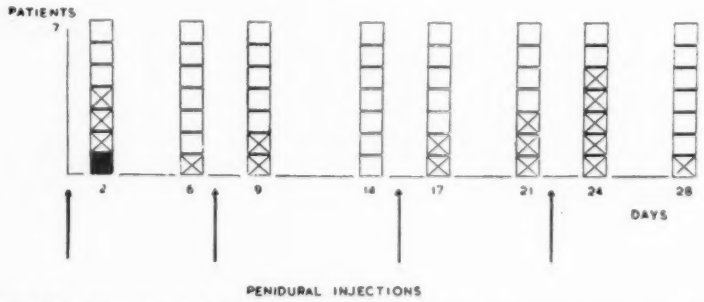

FIG. 3.—Penicillin blood levels in 7 patients receiving Penidural by weekly injections of 15,000 units per pound body-weight.

standard dose of 10,000 units per pound body-weight was given on 82 occasions, and caused local tenderness and induration for more than forty-eight hours in only 4 instances, but the larger injections of 15,000 units per pound produced disproportionately more discomfort with induration lasting over a week on 7 of the 28 occasions it was administered.

No frankly allergic reactions were observed in any patient but fever with anorexia and headache occurred regularly in 3 of the 7 children receiving the larger dose. This did not continue beyond the day following injection.

No clinical streptococcal infections were detected in any patient.

Penicillin assays: The range of serum-penicillin levels found in each group are shown in Figs. 1, 2, 3.

We regard 1/16th unit per ml. as a level safeguarding streptococcal prophylaxis, as well as preventing to a reasonable extent the emergence of penicillin-resistant staphylococci, and have depicted estimations falling below this in black. After a single injection of 10,000 units per pound body-weight almost half of the blood levels were deficient by the second week, and only 5 out of 17 showed inhibitory levels at the end of three weeks.

Weekly administration of the same dose maintained satisfactory levels in most but not all patients while the larger amount of 15,000 units per pound gave a satisfactory level in all 7 children tested.

Throat swabs.—Administration of Penidural did not eradicate beta-hæmolytic streptococci from the throats of children in any group possibly owing to dilution of the concentration of penicillin on the mucous surfaces of the throat by the continuous flow of saliva. The 17 children who had received one injection were swabbed 102 times with 54 positive results. During the third week after injection 12 out of 17 carried streptococci in their throats.

Approximately one-third of the throat swabs taken from children receiving weekly injections grew beta-hæmolytic streptococci; 37 out of 117 receiving 10,000 units, and 18 out of 56 receiving 15,000 units per pound body-weight.

Sensitivity of the streptococci to penicillin was determined in every case, but only rarely were relatively insensitive strains encountered (14 out of 105 positive cultures were only sensitive to concentrations of up to 2 units per ml.), and these were confined to few patients. No clinical infections due to other penicillin-resistant organisms were observed.

Conclusions.—These observations suggest to us that the bulk of Penidural which can be repeatedly administered intramuscularly to children is limited by local discomfort to approximately 10,000 units per pound body-weight, and that to maintain effective blood levels weekly administration is required.

Acknowledgments.—The authors are most grateful to Professor W. S. Craig for permission to treat patients under his care and to Messrs. John Wyeth and Brother Ltd., for generous supplies of Penidural and Mr. A. Myers for technical assistance. One of us (K. Z.) is indebted to the Medical Research Council for a grant in aid of expenses.

Constrictive Pericarditis in Early Childhood.—PROFESSOR C. W. VINING, M.D., F.R.C.P., D.P.H.

A male infant who developed sustained congestive heart failure after a respiratory infection at the age of 2½ years.

The original illness suggested pertussis but five weeks later the abdomen became distended by ascites and the child cyanosed and dyspnœic. X-ray examination showed mediastinal congestion accompanying a pericardial effusion. The subsequent course was that of intermittent and finally sustained congestive heart failure. By the age of 4 years the infant was permanently œdematous with only brief relief from abdominal paracentesis. Radiologically the heart shadow was not enlarged but appeared relatively inactive. The clinical diagnosis of constrictive pericarditis was supported by the sustained right atrial pressure during cardiac catheterization and confirmed at operation (Mr. G. H. Wooler). The patient has now returned to normal health.

The nature of the pericarditis has not been discovered. Tuberculin skin tests, and examination of the ascitic fluid for tubercle bacilli were consistently negative, while the histology of the thickened pericardium was non-specific. A moderate hypoproteinæmia (total 4·7 grams per cent) had developed before operation.

Congenital Hypophosphatasia.—R. L. LANGLEY, M.D., F.R.C.P.Ed.

This was the child referred to by Dr. B. E. Schlesinger at a previous meeting of the Section, when he (Dr. Schlesinger) showed a case of hypophosphatasia (Luder, 1954, *Proc. R. Soc. Med.*, **47**, 541).

Visceral Eosinophilia.—T. MORTON STEWART, M.D., D.C.H.

H. T., male, born 18.9.51, aged 3½ years.

On admission (21.4.54).—Pale, fretful, hypotonic. Liver enlarged three fingerbreadths below costal margin. Spleen just palpable. Glands palpable in neck, axillæ, groins. Purpura—feet and ankles.

Investigations.—W.B.C. 28,000 (neutros. 11%, lymphos. 23%, eosinos. 66%), Hb 64%. W.R. negative. X-ray skull and long bones normal. X-ray chest, bronchiolitis. Urine normal. Bone marrow intensely cellular. Van den Bergh: direct and indirect, negative; serum bilirubin >0·2. Serum proteins: albumin 3·1; globulin 6·7%. Biopsy of gland: non-specific inflammatory reaction. Stools repeatedly negative for parasites or ova. Liver biopsy: white nodules all over liver surface; microscopy—granulomatous reaction. Toxoplasmosis negative.

Progress.—During first few months in hospital, eosinophils varied from 84% to 39%. The rise in eosinophils corresponded with episodes of fever with purpura. He later developed right-sided heart failure, and eosinophils dropped in number. Died 31.5.55.

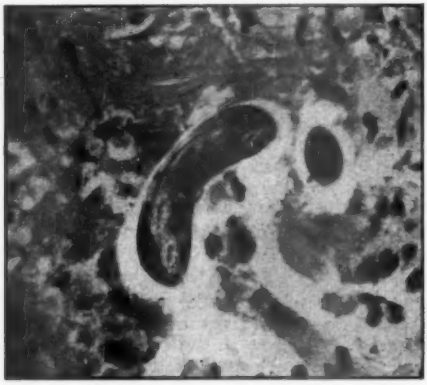

FIG. 1.—Section of lung showing larva. ×400.

Post-mortem.—Lungs: On surface of both lungs, white small miliary nodules, 1 mm. in diameter, approximately 40 in each lung. Several large infarcted areas at the periphery.

Circulatory system: Free fluid in pericardium. Hypertrophy and dilatation of right ventricle. Valves normal. One white nodule on endocardial surface of right ventricle.

Alimentary system: Liver enlarged, and on surface scattered white spots similar to those on lungs. Alimentary tract normal.

Histology.—Nodules were found in the substance and on the surface of lungs, liver, myocardium and pancreas. On section of lung one small parasite seen. This resembled the larval form of a nematode (Fig. 1). This was surrounded by a zone of endothelioid cells, and at the periphery a heavy infiltration of lymphocytes and eosinophils. Other nodules were examined and those showed a similar structure but no parasite was identified in them. Lungs showed venous congestion, and small pulmonary arteries with thickening of the walls, and narrowing of the lumina.

Myotonic Dystrophy.—E. C. ALLIBONE, M.D.

J. N. B., male, born 12.5.42, aged 13. Had been well until he had an illness four years ago originally considered to be poliomyelitis, but symptoms were compatible with those of polyneuritis. He had never made a complete recovery, remaining weak. Two years later muscular cramps became noticeable, aggravated by using the muscles, but also coming on spontaneously and even waking him up in the night. The cramps were more marked in cold weather. During the last twelve months he had had hunger pains relieved by food. His hair had stopped growing and had begun to fall out over the back of his head and the hair of his eyebrows had disappeared.

The patient was a very tall, thin boy. The skin of the body, limbs and face was hairless. There was thinning over the occiput. On examination of the skeletal system there was symmetrical wasting of the small muscles of the hand and forearm. There was asymmetrical

wasting of the sternomastoids, the right side being more affected. No trophic changes. Tendon reflexes present. From time to time cramps were observed, and these could be elicited in isolated muscle groups by percussion.

Investigations.—X-ray of stomach and duodenum normal. Rehfuss test meal showed hyperchlorhydria with delay in emptying. ECG normal. Electromyogram: Dr. D. Taverner. The right tibialis anticus and right flexor sublimis digitorum muscles were both normal.

Blood electrolytes: Serum calcium 10; phosphorus 4·1; sodium 320; potassium 14 mg./100 c.c. Serum alkaline phosphatase 11 K.A. units; CO_2 combining power 58 c.c. CO_2%. No porphyrins were detected in the urine.

Testes normal. Intelligence normal. Family history negative.

Treatment.—For the past six months had received quinine sulphate 3 grains t.d.s. with partial relief. When this was replaced at the parents' request by calcium lactate 10 grains t.d.s. there was a prompt relapse.

Fibrocystic Disease of the Pancreas with Hypoproteinæmic Œdema in Early Infancy.—WALTER HENDERSON, M.D., F.R.C.P.Ed., D.C.H.

P. D., male, born 19.4.54, aged 13 months. Birth-weight 5 lb. 8 oz. First child.

Admitted hospital 15.6.54 for investigation of occasional vomiting and of recently noticed peripheral œdema. Fully breast-fed, weight gain at first reasonable (3–4 oz. weekly) and latterly more rapid (7 oz. weekly).

On examination.—Well marked œdema of the face, of the legs from knees downward, and of the sacrum. No ascites. No skin lesions. Urine showed no abnormality.

Blood.—Total protein 2·9; albumin 1·45, globulin 1·45 grams%; urea 26, cholesterol 122 mg.%; Hb 90%.

Stools were recorded as often green, sometimes yellow, and not thought to be offensive.

Diagnosis.—Idiopathic hypoproteinæmic œdema. As the baby was still breast-fed and took its feeds reasonably well it was allowed home under supervision.

Progress.—The œdema persisted for a few weeks before gradually disappearing altogether —without specific treatment.

30.8.54: Blood protein, total 4·2; albumin 3·1, globulin 1·1 grams%.

Readmitted hospital 10.3.55, for investigation of slow weight gain and indifferent general health. Age now 10½ months. Weight only 9 lb. 15 oz. Best weight—at 9 months—only 10 lb. 12 oz. Recent tendency to chest infections and slight wheeze. Appetite voracious. Stools said to have been often loose and usually offensive. *Examination* showed no œdema, a full tympanitic abdomen, marked wasting, and a slightly emphysematous chest.

The diagnosis of Congenital Cystic Fibrosis of the Pancreas was confirmed by the following observations and investigations: The stools were characteristically offensive and had no trypsin; there was steatorrhœa with inadequate fat absorption (only 82% fat absorbed in a 6-day fat balance); the duodenal juice contained NO trypsin. There was a very satisfactory clinical response to specific treatment with pancreatin and a high caloric high protein diet.

Other investigations (6.6.55).—Blood protein 5·6; albumin 3·2, globulin 2·4 grams%. Blood urea 40 mg., cholesterol 90 mg.%. Serum alkaline phosphatase 36 K.A. units. Cephalin cholesterol flocculation +++.

Discussion.—The present clinical condition of the infant is quite compatible with the stage of improvement following specific treatment for cystic fibrosis of the pancreas. The hypoproteinæmic œdema of (roughly) the 5th to 15th weeks of life was apparently "idiopathic" and disappeared without specific treatment such as additional dietary protein. It is only rarely that hypoproteinæmic œdema occurs in cystic fibrosis of the pancreas though a very poor protein intake could be responsible; it seems hardly likely that such a low initial blood protein could have been raised without additional dietary protein, if it had been due solely to inadequate intake.

The suggestion of some impairment of liver function indicated by the raised serum alkaline phosphatase and abnormal cephalin cholesterol flocculation result hardly justifies serious consideration of the diagnosis of Hypoplasia of the Exocrine Tissue of the Pancreas as in the cases described by Lumb and Beautyman (1952) *J. Path. Bact.*, **64**, 679).

Two Cases of Hypervitaminosis A.—J. D. PICKUP, M.D.

Two children were shown who had received very high doses of Vitamin A for ichthyosis. Both had produced typical signs of hypervitaminosis A, features of which were discussed.

(To be published in full elsewhere.)

Banti's Syndrome in Siblings Treated by Porta-caval Anastomosis (Two cases).—J. P. SWEETNAM, M.D., M.R.C.P.

Our knowledge of the disease has advanced little since Banti's description of the syndrome in 1894. In children the disease tends to be severe with particular emphasis on the fatal occurrence of hæmatemesis.

Case I.—Male aged 5½. Admitted May 1952 with a hepatosplenomegaly. Liver biopsy revealed a portal cirrhosis. March 1954 severe hæmatemesis. Portal venogram showed intra-hepatic portal venous obstruction with severe gastro-œsophageal varices. An end-to-side porta-caval anastomosis was performed by Mr. Geoffrey Wooler in April 1954.

Case II.—Female aged 7. Admitted in October 1953 and again in January 1954 with hæmatemesis and a hepatosplenomegaly. Portal venogram showed an identical picture to Case I. A side-to-side porta-caval anastomosis was performed by Mr. Geoffrey Wooler in March 1954.

Discussion.—The medical treatment of the disease is unsatisfactory. Surgical treatment does offer a possible freedom from recurrent hæmatemesis. The post-operative progress of these children has been encouraging. The hepatosplenomegaly is less marked. Each has gained over 7 lb. None of the neurological complications described in adults has been observed. The ætiology remains obscure. There are no family illnesses of significance. Tidy (1952) has stated that the disease is a sequel of Rh iso-immunization. The sera of the whole family were tested against a comprehensive panel of cells covering the Rh, MNSs, P, Lu, Kell, Lewis, Duffy and Kidd orders of inheritable blood groups. No abnormal antibody was detected.

Acknowledgments.—I am greatly indebted to Mr. Geoffrey Wooler for the surgical treatment of these cases. Although a recognized procedure in adults, these may be the first instances of such an operation in young children.

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BANTI, G (1894) *Sem. Médicale*, **14**, 318.
TIDY, H. L. (1952) *Brit. med. J.*, ii, 1.

Hæmangioma with Thrombocytopenia.—M. G. PHILPOTT, M.D., M.R.C.P.

C.M., female, born 16.11.53, aged 19 months.

Seen as out-patient by surgical colleague on 31.12.53 because of extensive nævus on left side of face, which was noticed soon after birth and had been increasing rapidly in size. Referred to radiotherapist. Before treatment could be arranged, on 2.1.54 sent into hospital as emergency with dyspnœa associated with sudden increase in size of nævus, and œdema of face and neck.

On admission the baby was desperately ill, anæmic, and respirations were very laboured. There had been extensive hæmorrhage into the nævus with much surrounding œdema. Hb 5·9 grams%; bleeding time 8½ min.; clotting time 8 min.

The condition improved a little in an oyxgen tent, but the nævus continued to increase in size, due to further hæmorrhage. Vitamin K, 10 mg. daily, was given.

On 6.1.54, 100 c.c. fresh blood given by drip into scalp vein. Developed signs of pneumonia and given intramuscular penicillin. On 7.1.54 developed some petechiæ and a large swelling on anterior surface of right chest. Hb 8·9 grams%; W.B.C. 16,000.

8.1.54.—Hb 6·2 grams%; platelets 10,000/c.mm. Further transfusion attempted unsuccessfully.

10.1.54: Petechiæ still appearing. Further hæmorrhage into nævus. Pædiatric advice sought. Platelets: 6,000/c.mm.

Cortisone therapy commenced (50 mg. stat., 25 mg. 12-hourly, i.m.), in an effort to increase blood coagulability. Further transfusion 100 c.c. fresh blood given by drip (cut-down).

11.1.54: Condition unchanged. Sudden death.

Autopsy: Extensive hæmangioma infiltrating tissues of face and neck; much extravasation of blood. Large hæmatoma on right chest. Microscopically the nævus was reported as being a simple hæmangioma, with extensive capillary hæmorrhage. Sternal marrow was normal.

REFERENCE

FRANKLIN, A. W., and WILLIAMSON, D. A. J. (1953) *Arch. Dis. Childh.*, **28**, 490.

BOOK REVIEWS

Polypeptides which Stimulate Plain Muscle. Edited by J. H. Gaddum, F.R.S., Sc.D., M.R.C.S., L.R.C.P. (Pp. viii+140; 33 illustrations. 15s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

This short and excellently presented book must indeed be welcomed. It is based on a symposium organized by Professor U. S. von Euler in Montreal in 1953. Under Professor Gaddum's editorship, the contributors to the symposium have since submitted material for the book. The contents cover a wide field and the title has been stretched to include a review by Ephraim Shorr of V.E.M. and V.D.M. which are considered probably to be proteins, but have pharmacological effects in some way akin to those of other substances considered. It is not possible to mention all of the fifteen chapters, but in addition to this, Braun-Menendez and Irvine Page contribute chapters on Hypertensin which will bring the reader right up to date. Another important article summarizes recent work on the chemical structures and other aspects of the neurohypophyseal hormones. The publication of the book raises one or two important issues. The reader will be impressed by the resemblance of substances described under different names, and Gaddum critically deals with the problem of this differentiation, although not yet isolated in pure form, in the opening chapter. The question of the production of artefacts must always be present in our minds. The use of the phrase "local hormones" has been revived since its proposal by Gaddum at the Royal Society in 1950, and is of special interest to the reviewer. The term appears totally inconsistent with the usually accepted definition of Sterling, who thought that a hormone should be a substance elaborated in one part of the body and carried to distant parts. Coining of the term "local hormone" raises the issue too of the relation of these locally acting substances to enzyme systems. How intimately must they participate in these systems to cease to be a hormone? The answer to this problem is still awaited in the case of substances already accepted as hormones. It must be wiser to refrain from such new terms when applied to substances whose physiological function is very much a topic for debate.

In its published form, the material greatly lacks the value of a general discussion, which has been omitted. In a controversial field the opinion of those other than the individual authors would be of great value. This deficiency is partly made good by the inclusion of a closing chapter by Gaddum who reminds us in it of several active substances apparently produced by the action of various enzymes on α 2 plasma globulins. Two of these polypeptides appear to mimic the action of vasopressin and oxytocin. The book can hardly be recommended to anyone who likes to close the cover with a feeling of complete understanding, but can be strongly recommended to readers of varied interest who wish food for further thought and stimulus for action.

Diseases of the Liver and Biliary System. By Sheila Sherlock, M.D.Edin., F.R.C.P.Lond. (Pp. xvi+720; 198 illustrations. 50s.) Oxford: Blackwell Scientific Publications. 1955.

Our understanding of diseases of the liver has progressed considerably in the last ten or twenty years. Thus a book which states the present position clearly and gives an extensive and well-selected bibliography, whilst remaining within a reasonable compass, is indeed welcome.

Although this book is mainly concerned with a single organ, it is written by a specialist who is also a general physician, and, as a result, the importance of disorders of the liver and their management are neither over-stated nor understressed.

The early chapters describe the anatomy and chemistry of the liver itself, and its relationship to the hæmopoietic system, together with critical consideration of the methods available for investigating its function. The chapter on the uses and technique of needle biopsy is specially worthy of mention, as would be expected from a knowledge of the author's work.

There follows an excellent discussion of the conception of hepato-cellular failure, with its curious clinical features, including the comparatively recently recognized neurological complications of liver disease and the mechanism that underlies them. The management of these cases is fully discussed, and recent change of opinion in treatments is exemplified by the control of ascites. This can no longer be stated in a single sentence, as the propriety of the traditional paracentesis is questioned. Evidence is advanced for advising a determined effort to restrict salt and increase protein intake, and the practical difficulties are discussed.

The anatomy and methods of investigation of the portal vein and of the hepatic arteries

and vein by angiography and catheterization precede the description of the clinical states in which knowledge of these matters has relevance. This is a most helpful arrangement.

The recent advances in the surgery of portal hypertension are usefully summarized and neatly illustrated.

Since relatively little progress has been made recently in the study of the gall-bladder and bile passages, only a small part of the book is devoted to them. The necessary information is, nevertheless, included, and there is a well-illustrated section on the recent technique of cholangiography.

The book is attractively laid out and the illustrations and diagrams are clear and helpful, with the exception of the figuring on the large coloured diagram of the liver structure.

The Diseases of Occupations. By Donald Hunter, M.D., F.R.C.P. (Pp. xvi+1046, 438 illustrations. £5 5s.). London: English Universities Press Ltd. 1955.

The outstanding books on occupational medicine, or indeed on any branch of medicine, appear like comets at infrequent intervals. Dr. Donald Hunter's "The Diseases of Occupations" is clearly outstanding, more particularly because it points the way along which the occupational health services should develop. He puts the emphasis on the clinical aspects of disease in relation to occupation. Statistics of morbidity and mortality are extremely useful within their well-defined limits, but the clinician usually has to establish the relationship between the disease and the occupation before the statistician can get to work and before preventive measures can be designed and put into operation. Nowadays there is a tendency to forget the importance of the clinician and to emphasize that of the statistician.

Dr. Hunter is one of those rare general physicians who take the trouble to go into factories and mines to see the conditions under which their patients work. Like his illustrious predecessors Ramazzini, Thackrah, Peacock, Greenhow and Oliver, he appreciates fully that occupational diseases cannot be studied only from the armchair or from the consulting room. Further, he has approached the subject historically in order to show what has been achieved and what yet requires to be done. He modestly says that his opening chapters "depict in a disjointed way something of the historical, social and economic background of the occupations which men follow". On the contrary, the reader will find a fascinating and connected account of the rise of the idea that a man's occupation, his social and economic circumstances, the geographical and political climates in which he lives, will all affect his mental and physical health for better or worse. He has some justifiably scathing remarks to make about the attitude of the ancient Greeks towards their worker-slaves, and also about early Victorian employers and their unthinking cruelty. The medical profession, or at least selected members of it, are shown in a good light for the part they played in the reform of factory conditions. On the other hand, the employers were not all bad and due weight is given to the reforming zeal of such men as Robert Owen and Jeremy Bentham, while the parts played by Sir Edwin Chadwick, Sir Robert Peel, Lord Ashley and others in public health and factory reform are discussed fully.

The eleven chapters dealing with the clinical and other aspects of the occupational diseases are extremely thorough and well documented. Nowhere, for instance, will the reader find a better account of all the various aspects of lead poisoning than in this book. This is not surprising, because Dr. Hunter for many years has been an international authority on the subject. Methods of manufacture are described in detail and well illustrated. Both the old and the new metals are discussed fully. The latest information about beryllium, cadmium and vanadium poisoning is given with illustrative case histories. In one chapter there is a brilliant survey of the causes of accidents and their prevention and in another he gives a masterly account of the pneumoconioses.

Dr. Hunter has kept in mind the importance of describing the chemical composition of the materials handled in various occupations. He says that where he has described at length the use in industry of such harmless substances as chalk and limestone, the object has been to stress the fact that dirty and dusty conditions of working are not necessarily dangerous to health. Again, he says that some of the subject matter refers to diseases which are rare or even obsolete. Accordingly he felt it worthwhile to describe phosphorus poisoning in detail. Since the book has been published, pneumoconiosis has been reported in limestone workers, and there have been some cases of phosphorus poisoning. The Berne Convention has eliminated phosphorus poisoning from the manufacture of matches, but phosphorus has other uses. His section on phosphorus poisoning is therefore timely and not by any means obsolete. Industrial practice is changing with great rapidity and bringing with it new health risks, but Dr. Hunter's book is as complete and as up to date as any textbook can be. It is bound to become a standard work of reference for many years to come.

Neuro-vascular Hila of Limb Muscles. By James Couper Brash, M.C., M.A., M.D., D.Sc., LL.D., F.R.C.S.Ed., F.R.S.E. An Atlas with 30 coloured plates. (Pp. xvi+100; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

This atlas sets out to give some accurate data on the sites and mode of entry of the principal arteries of supply in the limb muscles and to correlate the entry with that of the nerve(s). After giving a brief review of the literature of the subject, the author then, by means of simple line drawings, shows the site of entry of the nerve and arteries to each muscle. As might be expected there is considerable variation in different muscles and even in the same muscles. In some muscles a definite neuro-vascular hilum has been recorded in approximately 50% of them. In others this hilum is present in over 80%. In at least three muscles (biceps brachii, latissimus dorsi, and gastrocnemius) a neuro-vascular hilum is recorded in 90% of these. The information for each muscle is concisely arranged and the variations and previous observations recorded. This book is a useful ready-reckoner of data in this important subject and can be recommended to all interested in the details of neuro-muscular supply.

Diseases of Infancy and Childhood. Edited by the late Sir Leonard Parsons, F.R.S., and Seymour Barling, C.M.G. M.S., M.Ch., F.R.C.S. 2nd edition. (2 vols., illustrated. £8 8s. 0d.) London, New York, Toronto: Oxford University Press (Geoffrey Cumberlege). 1954.

When fifty-eight highly esteemed and learned doctors settle down to write a textbook for the instruction of fellow clinicians, the reviewer's task is easy. Sir Leonard Parsons originally planned the work as a compilation by authorities each on his own subject, and Professor Barling with Dr. Clifford Parsons' assistance has not varied the plan in the second edition. The authors, if everyone is not an authority in the sense of having made original contributions to or spent a lifetime in the study of his subject, do at least write with the authority of long practical experience and a thorough up-to-date knowledge of the literature. The result is a completely successful text of reliable and well-presented fact.

The arrangement of the book in sections is based largely on systems, and particularly interesting are those on blood and blood-forming organs, on congenital heart disease, on the neonatal period, and on the ear, the eye and the skin. To pick these out for special mention does not indicate any criticism of the rest, for the general level is very high indeed. This is a handsome book, and illustrations and text are in the best medical manner of the Oxford University Press. One misses a photograph of Sir Leonard Parsons.

The question arises, for whom is the book intended? The medical student would be well advised to read it and to buy if he can afford so large a price, and the family doctor will find it a really helpful compendium of modern pædiatric practice. The pædiatrician will learn much, even though he may not agree with every statement, from what is almost a "System of Disease in Childhood."

Fluid and Electrolytes in Practice. By Harry Statland, M.D. (Pp. xiv+206; 30 figures. 35s.) London: Pitman Medical Publishing Co., Ltd. English edition. 1955.

Like the other books in English on body fluids and electrolytes which have appeared in recent years this one is written as an introduction rather than a work of reference. The book is in two parts, the first on general principles, the second on their application to special conditions.

The first part begins with a lucid description of the distribution and movements of water and electrolytes in the body and of the normal gains and losses. The author clearly sets out why the major ionic constituents of the body must be measured in chemical equivalents and not by weight; he describes well the major disturbances of water depletion and salt depletion and their prevention after operation. He then deals with potassium and magnesium and with acid-base balance, but here the exposition is not of the same quality and the novice may have difficulty in separating the outstanding facts from less important detail and unestablished speculation. The problem of water intoxication is hardly dealt with adequately.

The second part is much shorter than the first and describes briefly the disturbances in fluids and electrolytes in disease of the heart and the kidneys, diabetic acidosis, diseases of children, burns, ascites from cirrhosis and toxæmia of pregnancy.

The subject as a whole has been made unnecessarily complex as an introduction and the administration of parenteral electrolyte solutions is certainly overemphasized. It is a pity the style is often spoilt by careless writing. The bibliography of 161 references is well chosen.

AMERICAN SURGERY

Surgical Forum. Clinical Congress of the American College of Surgeons, 1954. Vol. V. (Pp. xl+851. 70s.) Philadelphia and London: W. B. Saunders Co. 1955.

Mayo Clinic and Mayo Foundation. Collected papers, 1954. Vol. **46.** (Pp. viii + 843. 87s. 6d.) Philadelphia and London: W. B. Saunders Co. 1955.

These two volumes so admirably represent the two main parallel characteristics of present-day American surgery that they lend themselves readily to a combined review. The first thing that strikes a sympathetic British observer of American surgery is its energy, its freshness and its emphasis on youth. Though the academic organization of American surgery in its origins owed so much to the continent of Europe, and especially Germany, its development in the democratic climate of the New World has produced something quite different from the sometimes still too rigid hierarchies of continental surgery. Ideas abound, there are plenty of facilities for testing them, and they are critically and freely judged on their worth rather than on the authority of their originators. The volumes of the Surgical Forum are an expression of this characteristic, which has found its main home and nourishment in the great university hospitals. But parallel with this, and equally characteristic, is a more conservative trend; the trend which leads large numbers of Americans to decide to have their operations in large private clinics where practical experience and skill have been concentrated and organized; the trend that withholds judgment on ideas until they have been tested by a large experience; the trend that the annual volumes of the Mayo Clinic admirably illustrate.

In a review one can give only a brief indication of the varied subject matter of this latest volume of Surgical Forum, with its more than a hundred and fifty papers. As would be expected, more than a third of the volume is occupied with the most obviously advancing edge of surgery—the surgery of the heart and circulation. And a sentence in the first paper gives one of the keys in this advance. It reads: "We found preliminary animal work of great help in preparing for operation on the patient." In the hall of the Pantheon of surgery which houses the names of those who have rendered modern heart and vascular surgery possible, the central place should clearly be occupied by a magnificent statue of a dog, wrought by a modern Michelangelo. Among the papers in this section may be specially mentioned those on hypothermia as a means of open operations on the heart, crossed circulation experiments, the establishment of an anastomotic supply to the heart by direct implantation of the internal mammary vessels, and some studies on the mechanics of pulmonary embolism. Of papers in other sections which impressed may be mentioned several on metabolism, particularly steroid metabolism, a paper on the successful transplantation of a fœtal thyroid and parathyroids for post-operative parathyroid deficiency, and one on an attempt to reproduce experimentally the œsophago-gastric sphincter mechanism. The use of intravenous fat emulsions is discussed but does not yet seem to have been fully worked out, and the most striking note in this connexion is a cautionary one.

The number and variety of papers in the Mayo Clinic Collected Papers, too, renders any detailed review impossible, and each will dip according to his special interests. There are, as usual, a large number of papers embodying the great experience of the Clinic in the treatment of gastro-intestinal conditions. Worthy of note are those on the gastro-intestinal complications of cortisone treatment, particularly in an increased liability to perforation of peptic ulcers and of the colon in ulcerative colitis; a paper on duodenal diverticula which are thought rarely to be the cause of symptoms; and one on the morbidity of the operation of ileostomy. For the rest, there is a small but important section on cardiac surgery, and the amount of space devoted to it in this volume is probably a fairer indication of the numerical importance of cardiac surgery in actual surgical practice than the much bigger space devoted to it in the Surgical Forum. There are informative articles on the cytological diagnosis of carcinoma of the cervix and bronchus. Other articles which struck the reviewer were on unilateral blindness as a complication of anæsthesia in neuro-surgical patients, and a very wise discussion on "The difficult patient", in which Englishmen will be interested to read a quotation from an address by Sir Lionel Whitby.

Altogether, if the mythical personage so commonly met with on radio programmes were allowed to supplement his "Desert Island Discs" by only two books to represent the surgery of America in 1954, he could hardly do better than choose these two.

Section of Urology

President—Victor W. Dix, F.R.C.S.

[*May* 26, 1955]

Hæmaturia in Children

By G. G. Wyllie, F.R.C.S.

The Hospital for Sick Children, Great Ormond Street

Hæmaturia during adult life is a symptom which demands a meticulous urological investigation and we must be most reluctant to accept benign conditions, like prostatic hypertrophy or hydronephrosis, as being responsible. If a pyelogram is at all doubtful we proceed to aortography and have no hesitation in repeating the pyelogram. The diagnosis of "essential hæmaturia" becomes more rare as cases are investigated more thoroughly. The investigation, then, is the important thing; there is little difficulty in determining in which patients it is necessary, or in justifying it.

But hæmaturia during childhood presents a problem of another kind. Chiefly, this is because acute nephritis is common whilst tumours are more rare and relatively more easy to diagnose and because physical and mental immaturity make admission to hospital and the surgical investigation of a young child matters of greater responsibility. We cannot ignore the psychological trauma involved in the admission of children to hospital—especially of those under 5. Urological investigation then is attended by dangers which are seldom encountered in adult practice.

It is widely taught that symptomless hæmaturia in childhood should be considered as due to acute nephritis until proved otherwise and, as a rule, such children are seen first by physicians. Understandably, they tend to delay intravenous pyelography lest diseased kidneys are damaged further. Yet there are a number of less common, though important, causes of hæmaturia in which surgical investigations and treatment are necessary. In the recognition of cases in this latter group, and in determining the extent of the investigation necessary in an individual case, lie the greatest difficulties and it may be well to consider the position of the urologist in this matter.

The child whose hæmaturia is associated with granular casts in the urine, œdema and hypertension has Bright's disease and presents no diagnostic problem apart from the form or the stage of the disease.

It is when symptomless hæmaturia occurs without casts, œdema or hypertension that we are on less sure ground. Long-term follow-ups suggest that acute nephritis may occur with little if any constitutional disturbance, œdema, hypertension or oliguria and few or no casts in the urine. In attempting to distinguish this form of nephritis we must place most reliance on the urinary findings.

The bleeding in nephritis usually follows a regular pattern—obvious blood being present in the urine for several days and microscopic quantities for a matter of weeks. During this period it is the rule for every specimen to contain blood, the amount of which declines steadily if no exacerbation of the disease occurs. If, shortly after an episode of hæmaturia, no red cells are found in the urine, nephritis is unlikely and some other cause should be sought. Similarly, a marked difference in the degree of blood-staining from day to day, or the recurrence of hæmaturia which had stopped, should raise doubt about the diagnosis. Whilst it is true that in acute nephritis blood-stained urine may be passed for several weeks, nevertheless after three to four weeks an intravenous pyelogram should be performed if the diagnosis must by then be doubtful.

I shall refer later to a series of cases in which hæmaturia remains unexplained. It is noteworthy that in the group this symptom occurred erratically. In more than one third the hæmaturia was intermittent or repeated at varying intervals. In the remainder there was but one episode, sometimes lasting only one day, and frequently, when seen shortly afterwards, there was no blood in the urine on microscopic examination.

Some help, too, may be had from estimations of the amount of albumin in the urine. As a rule, it is less in other organic diseases of the urinary tract than in nephritis, and persistently more albumin than would be expected from the amount of blood present suggests strongly some form of Bright's disease.

In the type of case under discussion urinary casts, which must be sought in fresh, uncentrifuged urine, are found in small numbers or not at all. Only a few may be passed during some mild episodes of nephritis and, equally, casts may be in the urine in other conditions which damage the renal parenchyma, such as stone, nephroblastoma and tuberculosis. Therefore, unless there are a number of granular casts on one occasion or hyaline casts persistently present, it is unwise to place too much reliance on this factor in the diagnosis of hæmaturia.

From the patient's history much may be learnt but a factor of great importance is whether there has been abdominal or loin pain. Such pain is seldom present in the mild case of nephritis. In a significant number of some of the other disorders which cause hæmaturia some pain in the side occurs, and demands urological investigation.

Conditions which Cause Hæmaturia in Infancy and Childhood

In the neonatal period septicæmia is the most common cause. Much less frequently does hæmaturia occur in hæmorrhagic disease of the newborn. What is more relevant to this discussion is the condition of renal vein thrombosis with infarction. There is a fairly common form in which infarction is secondary to infection with dehydration but the symptoms and signs are usually obscured by the primary disease and it is seldom a urological problem. Of more importance to the urologist is renal infarction occurring shortly after birth in otherwise healthy infants. Typically on the fifth to seventh day sudden shock and hæmaturia are followed by rapid renal enlargement, usually affecting one kidney but sometimes both. The ætiology is obscure but anoxæmia may be a factor. We had recently in Great Ormond Street a baby born normally after an uncomplicated pregnancy who had, at birth, a weak cry, peripheral cyanosis and a large mass filling one loin and when urine was passed it was blood-stained. Nephrectomy was performed and thrombus removed from the renal vein and the inferior vena cava into which it had extended. The kidney was extensively infarcted. Unfortunately, this baby died following peripheral circulatory failure but we know that nephrectomy may be life-saving in the unilateral case if performed early and adequate measures to counter shock are taken.

Another cause of a very different nature is shown by a baby who began to pass blood-stained urine on the fourth day of life. He had severe hypospadias with a cleft scrotum and there was a firm mass arising from the pelvis. He was, in fact, a male intersex with hæmatocolpos, and removal of the rudimentary uterus and vagina were necessary to relieve the acute symptoms.

In older infants bleeding from a meatal ulcer is the commonest variety of hæmaturia. The bleeding usually takes the form of a few drops of bright red blood at the beginning of micturition as the scab is disrupted, or at the end.

Hæmaturia associated with dilations of the upper urinary tract raises some interesting problems. A boy of 7 passed one blood-stained specimen at a time when he had an acute exacerbation of a chronic tonsillar infection and a temperature of 99° F. There were no casts, pus cells or excess protein in the urine but his blood pressure was 130/80. However, an intravenous pyelogram showed bilateral hydronephrosis of the type associated with obstruction at the pelvi-ureteric junction. One cannot be sure which factor was responsible.

Equally, a dilated ureter may be responsible for hæmaturia. A boy of 4 passed blood-stained urine two days after a squint operation. There were no casts or organisms in his urine and his blood pressure was normal, but pyelography showed dilatation of one ureter without hydronephrosis. Repeated pyelograms have not shown any further dilatation and there has been no further bleeding.

A boy of 6½ had hæmaturia, slight pain and a hard swelling in the loin, and a silent pyelogram on the same side. A tumour was suspected but retrograde pyelography revealed gross hydronephrosis and some months after a conservative operation on the pelvis of the kidney an intravenous pyelogram showed satisfactory function.

Whilst complicating stones or infection often are responsible for hæmaturia in hydronephrosis I think we must accept that, in children, this symptom may occur in uncomplicated cases. Presumably, then, vascular congestion at or above the site of the obstruction is responsible.

Hæmangiomata are common congenital anomalies but they rarely cause hæmaturia. The reported finding of blood-vessel malformations of microscopical proportions in kidneys removed for persistent unilateral bleeding is of interest in any consideration of the causes of hæmaturia. It may be well, though, to reserve judgment until post-mortem specimens have been extensively examined in a similar way.

At all ages during childhood urinary tract infections may cause hæmaturia just as in adult life. But whereas in the latter urinary symptoms are prominent, in infants they may be few and hæmaturia may then draw attention to the true nature of the illness. On the other hand drugs used in the treatment of an infection may be responsible. The response to treatment is the best guide to whether further investigation is necessary, for persistent or recurrent pyuria demands the exclusion of congenital anomalies and tumours in the urinary tract.

Urethritis in boys may cause urethral bleeding and probably the passage of blood-stained urine. We have treated a 9-year-old boy who had a blood-stained urethral discharge after micturition but no other symptoms. Cystoscopy showed a normal bladder but on urethroscopy the anterior urethra was reddened and rough with some adherent mucus. He responded to Gantrisin and alkalis though the bleeding continued for several months.

Tuberculous infection of the urinary tract may cause hæmaturia but so rare is this disease in children that it may be overlooked. In ten years at Great Ormond Street Hospital there have been 8 cases of which 6 had hæmaturia.

In children urinary tract calculi cause hæmaturia with perhaps greater frequency than in older age groups but the hæmaturia bears much less relationship to pain. Colicky pain is unusual and bleeding is commonly painless. On the other hand, pyuria is frequently present—it is, in fact, the most common mode of presentation of urolithiasis in childhood and most of the cases with hæmaturia have infected urine. This fact, and the absence of pain, suggests that infection may play an important part in the production of hæmaturia in calculus disease.

Hæmaturia during treatment of a throat infection with sulphonamides has occurred most commonly with sulphamerazine emulsions in our series. The bleeding may not necessarily be caused by the drug and the urine should be examined carefully and the blood pressure estimated, for glomerulo-nephritis or embolic nephritis may be the true cause. Whilst the finding of casts or crystals in the urine is not absolutely diagnostic, one without the other is an important indication and this examination should be done whenever hæmaturia occurs during treatment with sulphonamides.

There is nothing special about traumatic hæmaturia in children except that it may occur with relatively more trivial injury than in adults.

A plain X-ray is a necessary part of an investigation, e.g. to demonstrate a foreign body. A child of 3 years had several episodes of hæmaturia and pyuria dating from the time of an influenzal attack. Nephritis was suspected but X-ray showed a foreign body, like part of a hair-grip, to the right of the lumbar spine and after its removal from the vicinity of the ureter the bleeding stopped.

Of tumours responsible for hæmaturia, nephroblastoma is the most common. Most growths are seen in the first three years of life at a time when nephritis is uncommon, and at this age most Wilms' tumours which bleed into the urinary tract are palpable when the child is relaxed. But the diagnosis may be much more difficult in an older child. One boy of 5½ developed painless hæmaturia two weeks after a slight cough. His blood pressure was found to be 120/70, the blood urea 74 mg.%, and his urine contained albumin, blood

and casts. The blood disappeared after one week of bed rest, limited fluids and a low protein diet but recurred three weeks later whilst still in bed. Still a few casts were present. As his hæmaturia persisted an intravenous pyelogram was done. This showed a deformed pelvis and, at operation, a large Wilms' tumour was found.

In the series at Great Ormond Street Hospital hæmaturia occurred in 26% of cases of nephroblastoma and was the presenting symptom in 22%.

Of bladder tumours, rhabdomyosarcoma is the most frequently seen, but hæmaturia is uncommon. Retention and urinary infection are the usual modes of presentation.

There has not been a case of villous papilloma of the bladder at Great Ormond Street though the condition has been reported.

Whilst children with the conditions I have listed become the urologist's responsibility they may be seen first by the pædiatrician. Equally a surgeon may be the first to see a child whose hæmaturia is the initial feature of a general disease—leukæmia, purpura, infantile scurvy, hypoplastic anæmia, subacute bacterial endocarditis or polyarteritis nodosa. Examination of the blood may help, then, with the diagnosis but the diagnosis of some of these conditions is a clinical one, such as the exanthemata, gastro-intestinal disturbance and joint symptoms of Henoch-Schönlein purpura.

When all these conditions have been excluded as far as possible there remain a number of cases in which hæmaturia cannot be explained.

I have been able to find 46 such cases since 1939 in the records of Great Ormond Street but in the ten years since the war there were 38 cases and I think this figure gives a more reliable indication of their frequency. The ages ranged from 12 months to 11 years; one-third being under 3. There were no prominent symptoms though one-third had some abdominal or loin pain. None had more albumin or white cells in the urine than would be expected from the amount of blood. In 41 no casts were found whilst in 5 there were occasional casts, but insufficient for a definite diagnosis. 2 had temporarily raised blood urea levels but none had hypertension. Of the 46, 30 had been investigated to the extent of cystoscopy and retrograde pyelography and a further 5 had satisfactory intravenous pyelograms.

I have been able to trace 34 of these patients. In 26 there had been no recurrence of the hæmaturia, in 11 for periods of five to fifteen years and in 15 for less than five years, whilst in 8 cases there had been further hæmaturia. All were well. In most of the cases where bleeding continued this had occurred for a number of years, 8 in the longest instance, and was intermittent. One boy was sent to us still bleeding after he had had a nephrectomy in another hospital. He, like some others in this group, notices that it often occurs after exercise and it is difficult in these cases to know whether exercise should be restricted. There seems no convincing reason why it should.

It is possible that several conditions are represented among these 46 cases. It may be thought that the majority had had acute nephritis but there was a striking absence of symptoms. However, since the days of Sir Thomas Barlow it has been taught in Great Ormond Street Hospital that there is a hæmorrhagic form of acute nephritis which clinically resembles the pattern described.

Minute blood-vessel malformations in the kidney may be responsible in some cases but one would not then expect so many to stop bleeding.

Crystals in the urine were found in very few and in only one were oxalate crystals persistently found.

One could speculate for a long time. The important thing is to realize that many cases of hæmaturia in children, unexplained after adequate urological investigation, may have no further trouble for quite long periods and that it is unjustifiable to subject them to repeated surgical investigations.

The Management of a Child Alleged to have Passed Blood in the Urine

First, the history must be adequate. Drugs, such as sulphonamides, foods rich in oxalates, and substances containing red pigments, like beetroot and boiled sweets, may have been taken. Then it must be proved that blood is responsible and not hæmoglobin, urates or red pigment.

When urine and blood examinations, a straight X-ray of the abdomen, and physical examination are negative pyelography must be considered. Whilst intravenous pyelography should be avoided in acute nephritis, it appears to be harmless in this disease when it is so mild that the diagnosis is doubtful. With care and patience an intravenous pyelogram can be performed in infants and children of all ages and it is important to obtain good-quality

pictures. In some cases, especially girls, a good excretion pyelogram may enable one to dispense with cystoscopy, for local lesions of the bladder are very uncommon. With boys, on the other hand, cystoscopy and urethroscopy are usually necessary.

If all these examinations are negative the urological investigation may reasonably be suspended for a time. Provided the loins are felt regularly and carefully a bleeding nephroblastoma should not be overlooked.

If the hæmaturia persists or recurs the intravenous pyelogram should be repeated before the cystoscopy and two months is a reasonable interval if the initial examinations were satisfactory and negative.

There is rarely any worth-while information resulting from urological investigations repeated after, say, two satisfactory cystoscopies and pyelograms, yet one sees children with recurrent episodes of hæmaturia who have been subjected to numerous surgical investigations over long periods.

My review of these problems has had to be brief and I have not mentioned some conditions which may be concerned in this matter, but I have tried to indicate that adult standards should not be applied to this problem, for thereby much harm may be done to the child.

I wish to thank the physicians and surgeons of the Hospital for Sick Children, Great Ormond Street, for allowing me to use their cases in this investigation, and particularly Professor A. A. Moncrieff for his advice. But especially must I thank Mr. D. Innes Williams who suggested to me this paper and gave me the greatest possible help in its preparation.

Mr. Geoffrey Parker asked the author to comment on granular casts of the kidney. He had a patient, a boy of 5, who had flakes of blood in the urine, but the child, who had been referred to a pædiatrician, was not ill. Would Mr. Wyllie expect to find in routine cases the presence of granular casts in the urine?

Mr. Ashton Miller said that there had been 25 cases of hæmaturia at the Bristol Children's Hospital during the last five years. Nearly half had had painless hæmaturia for which, in spite of all investigations, no cause had been found. 4 others were due to mild renal trauma, and 9 to sulphonamides including 6 cases of ureteric blockage.

Mr. Edgar Freshman said that he had had 2 cases sent to him at the Royal Sea-Bathing Hospital in the last six months by very thorough surgeons who had not been satisfied with the results of examintion of three early morning specimens of urine. The tubercle bacillus appeared in one case in the fifth specimen and in the other in the sixth. There were no symptoms whatsoever, and the intravenous pyelograms were normal. One should not exclude renal tuberculosis in children without the most persistent investigation.

Mr. H. G. Hanley noted that Mr. Wyllie's physician colleagues were averse to performing excretion urography in children suspected of having nephritis, but was there any evidence that pyelography was dangerous in such children?

Mr. F. J. Milward asked whether, in the investigation of a child whose only symptom was a single attack of hæmaturia, one should have an intravenous pyelogram done after a month. If this was negative did Mr. Wyllie consider it necessary to carry out a cystoscopy, or should one wait to see if the bleeding was repeated?

Mr. Wyllie, in reply, said that granular casts were not a usual finding in nephroblastoma: he had mentioned them as a diagnostic problem, a warning of what could occur. He agreed with what had been said about trauma. In reply to Mr. Hanley, Mr. Wyllie said that in the absence of hypertension, œdema and casts, he did not think pyelography was dangerous.
In reply to Mr. Milward, if the pyelogram was negative after a single attack of haematuria cystoscopy could be delayed.

Surgical Pyuria

By A. Ian L. Maitland, F.R.C.S.Ed., F.R.F.P.S.
Royal Hospital for Sick Children, Glasgow

Pyuria is common in childhood and often due to transient cystitis or pyelonephritis. Where resistance to treatment is evident or a tendency to relapse is present the primary cause may be amenable to surgical treatment and it is with these cases that this short communication deals. Hydronephrosis is not included as it usually presents as an abdominal

colic and not as a pyuria; nor is renal phthisis, for this is rare in children and invariably follows a recognized primary focus. It should, however, always be excluded in a patient presenting with pyuria with no obvious associated organisms.

There are 9 cases for presentation: all had pyuria and 2 presented with overflow incontinence. They have been divided into two groups, those in which the principal lesion was in

FIG. 1.—Pre-operative intravenous pyelogram showing the gross dilatation of the upper renal tract and bladder in Case I.

FIG. 2.—Post-operative pyelogram of Case I showing the slight degree of improvement which has taken place.

FIG. 3.—Pre-operative intravenous pyelogram (September 1953) showing the large diverticulum of the bladder with a functionless right kidney in Case IV.

FIG. 4.—Intravenous pyelogram of August 1954 showing the return of function and fairly normal outline of the right kidney which resulted from the treatment (Case IV).

the lower urinary tract forming one and the other comprising abnormalities affecting the upper urinary tract.

All the cases affecting the lower urinary tract had congenital valves in the posterior urethra but 3 had additional abnormalities as well. They were all male children.

FIG. 5.—Intravenous pyelogram showing the enormous size of the bladder and severe dilatation of the right kidney in Case III.

FIG. 6.—Intravenous pyelogram showing a reduplicated and greatly dilated ureter on the left side. The lower normal part of the pelvis can be seen lateral to the upper knuckle of the dilated ureter (Case V).

FIG. 7.—Intravenous pyelograms showing poor function and fragmented outline on the right side (Case VI).

FIG. 8.—Retrograde pyelogram of the same case showing the small and distended upper element (Case VI).

4 of the cases demonstrated showed in the first and second, continuance of the dila ation of the ureters and renal pelves in the absence of physical obstruction; in the third, co plete recovery of the remaining kidney after valves, contracted bladder neck and an e topic megalo-ureter had been treated, and in the fourth case, good recovery was shown in both kidneys after fulguration of valves, excision of bladder neck and removal of diverti ulum with reimplanting of the associated ureter.

FIG. 9.—Retrograde pyelogram of the lower normal pelvis displaced by a pyonephrotic upper pelvis (Case VII).

FIG. 10.—Retrograde pyelogram showing the strictured and dilated ureter in Case VIII.

FIG. 11.—Intravenous pyelogram showing the filling defect in the bladder due to a large ureterocele with poor or absent function of that kidney.

FIG. 12.—Ten-minute emptying film of the right side in Case IX after transvesical excision of the ureterocele showing the enormous megalo-ureter and hydronephrosis present.

The behaviour of the cases in this group shows the dangers of recurrent infection, that episodes of retention occur after relief of all visible physical obstruction as described by Swenson, and lastly the tendency for congenital lesions of the urinary tract to be multiple.

5 cases of abnormalities of the upper urinary tract and ureter were then shown. They comprised a hydronephrosis and hydro-ureter, the upper half of a double kidney with function, and a similar case in which there was no function. In the second case of this group (Case VI) the upper renal pelvis was small and the seat of atrophic pyelonephritis.

The ureteric abnormalities shown were: congenital stricture in the middle and at the vesical orifice of the same ureter, and a very large megalo-ureter caused by a large ureterocele, treated by resection of ureterocele and the middle third of the ureter in two stages.

The points made were that in the cases of re-duplication of ureter and renal pelvis diagnosis is easy when function is present; when it is not present it may be extremely difficult without an exploratory operation. Conservative methods had been used in both cases of enlarged ureter with the establishment of good physical drainage, in spite of this the pyuria persists and it is probable that nephro-ureterectomy may still be required. Even so, it is felt that conservative methods are best in such cases owing to the danger of a latent contralateral abnormality giving trouble in later life.

In conclusion it is hoped that this short presentation will have revealed the difficulties which may occur in the diagnosis of the basic cause of pyuria in children and that the problems of management have been clearly displayed.

Lastly I should like to express my thanks to Professor Stanley Graham and Dr. J. Holmes Hutchison for referring some of these cases to me; to the Radiologist, Dr. S. P. Rawson, for the radiographs and to Mr. J. L. A. Evatt, the Department of Medical Photography, for the reproductions.

REFERENCE

SWENSON, O. (1955) *Arch. Dis. Childh.*, **30**, 1.

Mr. Thomas Moore asked whether the author had not found that the commonest type of case which had recurrent pyuria was the child with a unilateral or bilateral dilatation of the ureter without any organic obstruction. What did he do in such a case?

Mr. Alex. E. Roche asked whether a form of ureteric achalasia accounted for dilatation of the ureter, in the absence of obstruction to a catheter; whether it was not sufficient in some cases and less risky to remove the kidney and only part of the ureter, rather than the whole of it: and whether, as a lesser alternative to nephrectomy or nephro-ureterectomy, one might not, in selected cases, anastomose the dilated ureter to the bladder.

Mr. N. L. Shepperd said he was interested in Mr. Maitland's case in which the pyelogram showed that after removing the bladder-neck valve megalo-ureters persisted. These megalo-ureters had a separate ætiology, neurogenic in origin, and were vastly improved after bilateral ureterolysis.

Mr. Maitland in reply to Mr. Moore's question on bilateral dilatation of the ureter, stated that there could be obstruction at the ureteric orifice. In reply to Mr. Roche the catheterization of the ureter had not been difficult. He thought on the second point Mr. Roche had raised that the pædiatricians tended to push the surgeon when the latter would probably prefer to delay intervention. Cases VIII and IX demonstrated the doubtful value of conservative treatment.

Anastomosis of the dilated ureter left the dilatation, and most surgeons preferred to remove it, although one could always try an anastomosis or resection of a part and, if necessary, resect the kidney later.

Anatomical Abnormalities Found in the Urinary Tract of Enuretics, their Significance and Surgical Treatment

By GEORGE D. F. MCFADDEN, M.Ch., F.R.C.S.

THE problem of enuresis is a serious one and one which has hitherto seemed insoluble.

The adult enuretics hide their defect. It is only in such times as war that the medical world learns of the number of adult sufferers by the number of enuretics amongst the conscripts.

The sufferer may never have attained normal continence. He may have acquired normal night continence and remained so for several years, then this normal period has been succeeded by the onset of nocturnal enuresis which has remained permanent. In a number the period of wet nights is succeeded by a period of dry nights. Some have associated frequency of micturition during the day. In some the nocturnal enuresis only occurs at odd times in an

apparently normal person. Some cases have associated loss of bladder control dur ng the day; some, besides loss of bladder, have loss of rectal control.

From the anatomy and physiology of the bladder control it is clear that the func on of the bladder will be affected by a lesion or defect in any part of it from the cerebrum o the bladder outlet. In the brain there is suggestive evidence that there is an inhibitory entre for the bladder near the leg centre as well as a centre for tone in the mid-brain and p ssibly an excitatory centre. The result of the involvement of the nerve tracts in controlli g the spinal cord at different levels is well known and also the results of lesions of the paras mpathetic and sympathetic pathways. The bladder musculature, the competence o the sphincters and the question of obstruction to the outflow from the bladder must be consi dered. Over all psychic factors may be dominant. The whole symptom complex must be analysed and the seat of the lesion determined so that appropriate treatment m y be undertaken.

From our investigations abnormalities in the mechanism of the bladder sphincter brought about by obstructive and nerve lesions play a larger part in the production of enuresis than has hitherto been acknowledged (Fisher and Forsythe), and these enuretics must be treated surgically. Using the modern endoscopic instruments and the opaque barium technique of cysto-urography, for which I am indebted to Dr. Ian Forsythe, some 300 cases of persistent enuresis have been investigated. It was found that about 50% of the boys and 40% of the girls had abnormalities of the urinary tract, as follows:

Neurogenic	14	Small capacity bladders with associated trabeculation, probably obstructive, in process of investigation	8
Obstructive:		Vulvo-vaginitis	1
Valves in post. urethra	58		117
Wide bladder neck in female ..	27	Dilated ureters and hydronephrosis	4
Meatal stenosis—girls	3	Infected urine	4
boys	1		
Perineal stenosis	1		
Bladder-neck obstruction	3		
Double terminal urethra	1		

These results do not quite conform to those of other investigators. For example, residual urine was not encountered in the case of valves; this is contrary to what is commonly accepted as one of the signs of valves in the urethra. These patients can empty their bladder. These valves are not the diaphanous membrane commonly seen in museums but thickish folds of mucous membrane—exaggerated folds of the crista urethralis (Fig. 1). One can see that if the fold is causing a gross obstruction it will become stretched out and thin, and in this condition it is not far from the post-mortem room and thence to the museum. Sometimes one sees these diaphanous folds in museums apparently as low as the bulbus urethræ. Astley has shown by X-ray cinematograph that during micturition these folds are pushed down. That the urethral folds seen during urethroscopy are not just anatomical curiosities but cause definite resistance to the flow of urine is shown by the dilated post. urethra behind them and by trabeculation of the bladder that is practically always present and also by the frequency of diverticula encountered (Fig. 2). At first the effort needed causes a hypertrophy of the muscle of the bladder and trigone causing decreased bladder capacity and a narrowing of the vesical neck, but eventually the internal sphincter, if no infection supervenes, gives way and the wide bladder neck is produced (Fig. 3). The permanent narrowed bladder neck only present in 3 of our cases is probably due to superadded infection with resulting fibrosis and causing a submucous fibrous layer (Fig. 4). In our 117 cases infection of the urine was present in 4 cases, only mild in 1, and in the severe cases it is associated with dilated ureter. These dilated ureters are capable of contracting down and can show active peristalsis.

Burns, Pratt, and Hendon in a review of 81 cases state that there was bladder-neck contraction in 78 and only 3 post. urethral valves. Infection and residual urine were common but trabeculation not common. Helmholtz in a review of 49 cases of urinary incontinence at the Mayo Clinic also draws attention to bladder-neck contraction, 31 out of 49, of which 14 were enuretics. Infection was common yet he found no valves. He thought this was due to the fact that those with valves had probably died earlier in life. As far as I am aware none of these observers used the barium cysto-urethrography technique.

That the hypertrophied muscle at the bladder neck can return to normal once the obstruction is removed is shown by the increased capacity of the bladder after removal of valves. Also if the urine keeps free from infection and the obstruction persists the bladder neck will dilate giving an abnormally wide opening. This is still capable of returning to normal if the obstruction is removed in time, but if it persists it will be necessary to bring about mucosal apposition by operation before normal conditions are restored.

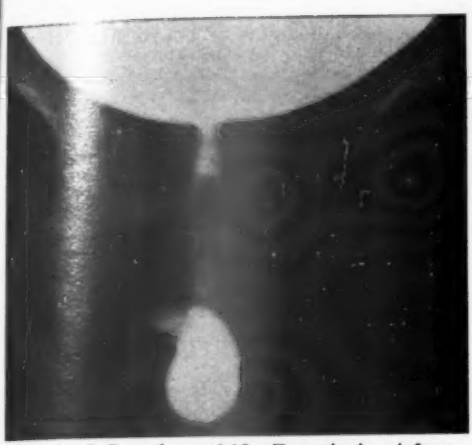

FIG. 1.—J. C., male, aged 15. Enuretic since infancy. Valve in post. urethra. No gross anatomical changes in bladder or internal urethral orifice.

FIG. 2.—Male enuretic. Valvular obstruction with dilatation and elongation of the posterior urethra and widening of sphincteric opening of bladder.

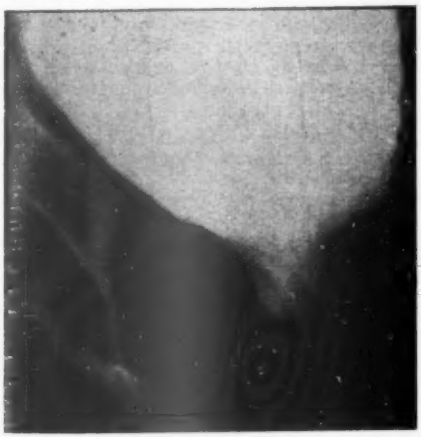

FIG. 3.—Male enuretic. Urethral valve with widening of bladder neck and dilated posterior urethra.

FIG. 4.—Male, aged 50. Enuresis and marked residual urine. Contracture of bladder neck with diverticula of bladder.

In many of the cysto-urethrograms the verumontanum shows up as a marked filling defect. Sometimes it would appear to me that this colliculus is more pedunculated than others and a protrusion down the urethra with the force of urine behind it abutting it against folds which, with a normal colliculus, would not hamper the stream, may be a cause of obstruction. Here the folds are removed.

Seen through the urethroscope the verumontanum varies in appearance, polypi may be present even in the child without any symptoms. If a prominent verumontanum is present and the case is one of enuresis without complications I prefer to leave it alone and await results. The chance of causing sterility is too high a price to pay for its removal.

Valves were not found in the urethra of girls, but a dilated urethra and internal orifice were common; 25 in all (Fig. 5). In some of these the external meatus was abnormal in that

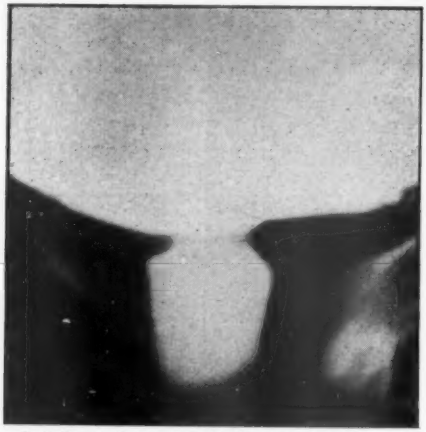

FIG. 5.—Female. Enuresis associated with meatal stenosis, dilated urethra and dilated bladder neck.

a fold passed across it from behind diverting the stream more forward. This has been commented on by Higgins. If a hook is passed up the urethra and dragged down it causes this post. fold to dip lower than the orifice, so we can see how a stream of fluid can, in these cases, produce a valvular obstruction. In 2 cases where this was the only abnormality found, removal of the fold cured a hitherto intractable enuresis. Some urethras would only admit the tip of a number 7 Charrière bougie. In others no external abnormality could be found, but, as urine is secreted from three months' intra-uterine life, any slight obstruction as sticking together of the labia could cause obstruction and widening of the urinary passage, as suggested by Higgins. There was one case of non-bacterial vulvo-vaginitis.

This dilatation of the internal orifice, the result of some obstruction, is to be distinguished from the dilatation that is neurogenic in origin. Here, instead of the rounded angulation between the bladder and the urethra in the cysto-urethrogram there is a smooth funnelling where the bladder shadow passes imperceptibly into that of the urethra. There were 5 girls and 8 boys with this condition. Spina bifida was associated with some of these—2 girls and 5 of the boys. In this group the patients were often normal for several years before enuresis developed. It takes some years before the relative length of the spinal column to the length of the dura mater becomes so pronounced as to cause pressure or a lipoma to grow sufficiently to press upon the spinal nerves, so late urinary symptoms might be expected. In some no cause was found. Fæcal incontinence was associated with urinary disturbance in 6 of the 8 boys and in 1 of the 5 girls.

The symptoms complained of are not definite enough to distinguish between the psychological and the physical cause of bed-wetting. Dribbling, straining, incontinence on laughing, and in a baby constant wet napkins point to an organic cause, but urgency, frequency, and even fæcal incontinence are common to both. The patient who has only occasional bouts of nocturnal enuresis is most probably psychological.

It is interesting that—except in the neurogenic variety—coughing, sneezing and straining do not cause leakage of urine, but laughing may. This is to be expected if the mechanism of the sphincter is considered. All sphincters connecting with the exterior have a common mechanism. If one takes a fresh stomach with œsophagus attached, fills the stomach with water and then inverts it, water will flow out through the œsophagus, but if the cardiac end of the œsophagus is gently gripped so that the mucosa is in apposition even so loosely that a catheter No. 12 can be passed easily through it, the cardia will resist the pressure of water—even that of a full pint. At first it seems strange that such a loose approximation could be so watertight, but on fuller consideration one recalls that this is the state of affairs of the bladder sphincter. A catheter can always be glided easily into the bladder. In other words, the sphincteric mechanism at rest does not squeeze the mucosa tightly but only keeps the mucosa of the sphincteric ring in gentle apposition. The involuntary sphincteric muscle

has only power to contract a specific amount. If there is an overstretched sphincteric ring, ma[illegible]eveloped mucosa, inefficient musculature, or when the mucosa is removed by trauma as after a rough prostatectomy, there will be lack of apposition of the mucosa at the sphincteric opening and, unless another mechanism is brought into action, incontinence will result. Now, an external sphincter has around it voluntary muscle to support it in times of stress and strain. The diaphragm exerts its pinchcock action at the lower end of the œsophagus; at the other end of the digestive tube the levator ani group surround and support the delicate sphincters of the rectum and bladder. If these voluntary muscles are torn, injured, paralysed, or congenitally misplaced, then stress incontinence supervenes. If on the other hand the involuntary muscle has lost its tone or has been continually overstretched so that mucosal apposition is not attained, continence may still be achieved by the tonic contraction of the voluntary muscle (Fig. 6). If a patient with this latter state, who is depending on his volun-

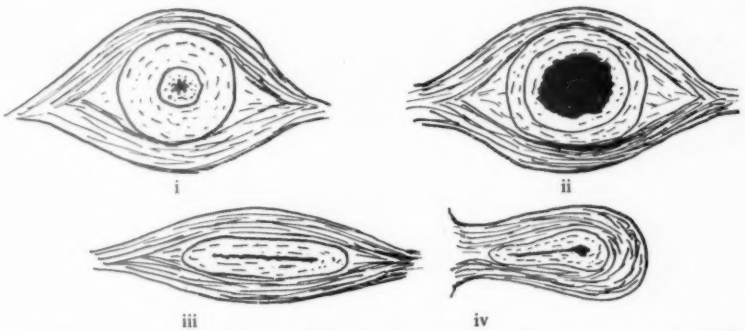

FIG. 6.—i. Diagrammatic. Normal: Mucosal apposition retained by tone of involuntary muscle. ii. Lack of mucosal apposition by involuntary muscle. iii and iv. Mucosal apposition obtained by voluntary muscle where involuntary muscle is insufficient to bring about mucosal apposition.

tary muscle for continence, falls asleep, the voluntary muscle relaxes and bed-wetting ensues. Laughing relaxes the voluntary muscle also—hence incontinence on laughing in some of our cases.

Physicians have tried to help the enuretic by prescribing drugs that help to keep him half-awake, or a child in a strange bed may not relax completely and have a dry night. When the mucosal defect is small, the passage of an instrument or a mere fulguration may swell the mucosa up sufficiently to keep it gently apposed for a time and so be followed by dry nights.

The following case appears to help in understanding nocturnal enuresis when due to defective involuntary muscle in the sphincteric mechanism. This child was born with a defect of the subumbilical part of the primitive streak. She had an ectopia vesicæ, no anal canal but two fistulous openings, one on each side and a spina bifida ventosa. This child could not be treated by transplantation of the ureters till a competent anal sphincter was constructed. First a colostomy was done to divert the fæces from the perineum and, although urine was constantly trickling over the perineal area, it was hoped by adequate nursing to get a healing wound. As in congenital dehiscence of any part of the body the embryonic elements are still present although misplaced, we proceeded to expose the perineum, the fibrous mid-band between the fistulous openings was removed and sphincteric apparatus constructed by bringing the levator ani behind and in front of the ano-rectal area and the remnants of the external sphincter on each side approximated. In this way a sphincteric mechanism was constructed. The rectum was then tested to determine if it would hold water. When the sphincter was found competent to hold water the colostomy was closed and the ureters transplanted into the colon and the ectopic bladder removed.

Now this child as a result of her operation developed good control during the day. She could go without evacuation and keep dry for three to four hours during the day and go to school and take part in all school sports without leakage, but this child when she fell asleep at night wet the bed; there was no fæcal incontinence. She had in other words nocturnal enuresis. The voluntary muscles used to contract the sphincter could keep the mucosa of the anal canal in apposition, but when this voluntary muscle relaxed in sleep the mucosa was no longer in apposition and water passed out.

We see a similar condition to be present in many enuretics; there is a lack of mucosal apposition by the involuntary muscle, but during the day this can be approximated by their

voluntary muscle, but in deep sleep with relaxation of their voluntary muscle urine passes out and the bladder is evacuated.

It was thought that an operation that would bring about mucosal apposition by the involuntary muscle might cure many cases of enuresis.

My first case was a young woman aged 25 who had never had a dry night in her whole life. It was very instructive. At operation the urethra was separated in the perineum from the vaginal wall and the urethral mucosa plicated with silk ligatures until the urethra was narrowed to a No. 7 English size catheter. In this way the mucosa was approximated. Next morning that young woman's face was like one transfigured—she had had a dry night for the first time in her life, and she continued dry for about three weeks. Then the enuresis recurred to our mutual sorrow. The urethra was then measured again, and it was found that the urethra was as large as before the operation or, in other words, the silk ligatures had cut through the tissues and the patient was in every way as before. It was then thought a retropubic approach to the urethra with a ligature of fascia lata tied round the whole circumference of the urethra at its outlet from the bladder tightly enough to hold firmly with a No. 7 catheter in position and the knot in the fascia lata fixed in position with silk ligatures would permanently narrow the urethra and bring about mucosal approximation. After this she was dry at night for the first six months in her life; then the enuresis returned. To see if the urethra could have widened again due to the fixation stitch of silk of the fascia lata giving way or whether our theory of nocturnal enuresis was wrong the urethra was measured again. It had reverted to its former size. A catheter No. 16 English could easily be passed. Here, each time the urethra was narrowed and mucosal apposition obtained nocturnal enuresis was cured. The method of cure of some cases of enuresis is now one of technique to produce a permanent narrowing to cause apposition of the urethral mucosa in the resting relaxed condition of sleep after all obstructions have been removed.

Drugs that depress the action of the pelvic nerves and leave the sympathetic unopposed increase the resistance of the sphincteric mechanism and thus increase the resistance to emptying. Jennings Marshall has attempted to do this surgically by severing the majority of the fibres entering into the pelvic nerves. It is noteworthy that some of our cases who did not react to Pro-Banthine before plastic operation did so afterwards. It is assumed that before operation the opening was too wide for the drug to cause any effect but that the extra contracture after the plastic operation was sufficient to keep the mucosa in apposition which it was unable to do before operation.

Frequently a psychological state comes to overshadow the physical one. Pavlov has stated the longer a conditioned response is maintained the harder it is to extinguish it. The child by its bed-wetting has seen the attention showered upon it and often uses it as a defence against its deficiencies and as an excuse for bad school reports. The psychological condition has been set in train by the physical one and not vice versa. The psychological factor must not be lost sight of when the physical abnormalities are overcome.

In enuretics that have resisted all previous medical treatment we find that in those cases with valves, roughly 43% are cured of their bed-wetting with one treatment, 45% are improved and in the short time of supervision 12% showed no change. In some the valvular obstruction may not be completely eradicated in one sitting, and in others the wide bladder neck has not yet had time to return to normal, and only time decides as to whether a plastic operation on the bladder neck may be necessary to bring about mucosal apposition. In others the marked psychological overlay has not been got rid of. It will take further time to get an accurate picture, as children improved may become cured or possibly vice versa.

The operation that I have been doing for some time in cases of bladder-neck dilatation aims at producing a permanent approximation of mucosa. In the first place all valves or obstructions are removed, then, through a retropubic approach a width of the muscle of the urethra down to the mucosa and extending up into the lower part of the bladder ending in an acute angle is excised leaving the mucosa intact. The cut edges of the muscle are then brought together causing inversion of the mucosa and producing a muscular ring firmly around it. To allow these edges to come together without tension, the pelvic fascia at the side is incised and the urethra slightly separated from the vagina. On account of the plexus of veins there is a fair amount of bleeding which can be tedious and adds to the difficulty of what aims at an accurate amount of excision and approximation. It is essential that mucosal apposition of the sphincteric opening should be obtained and removal of over half the circumference is usually necessary. A catheter—No. 5 or 6—which should be felt to be gripped, is tied in, after the manner of Harris, and the bladder closed. The mucosa, if torn, is sewn separately with plain 00 catgut and the muscle with silk or linen thread; a help in some cases is to tie a ligature round the whole urethra to ease the tension on the sutures. It is essential that all clots are removed from the bladder, as a small catheter is inclined to block and throw strain on the sutures. A drip should be in readiness, as many of these children are not over-robust. There have been no complications of the operation.

This seems a severe operation, but it is no more severe than that for stress incontinence in adults, and it is reserved for those patients with a wide bladder neck who are not regaining tone after an obstruction is removed and for the neurogenic cases. The results are encouraging (Figs. 7, 8, 9, 10).

FIG. 7.—Male, aged 16. Enuresis since infancy. Valve in post. urethra—dilated internal urethral orifice and post. urethra—treated by removal of obstruction and plastic operation on bladder neck.

FIG. 8.—McCl., male, aged 16 (same case as in Fig. 7). Micturating cystogram after operation. No enuresis since operation.

FIG. 9.—E. McC., female, aged 25. Enuresis since infancy. Enuresis cured by plastic operation on bladder neck.

FIG. 10.—E. McC., female, aged 25 (same case as in Fig. 9). Cystourethrogram following plastic operation on bladder.

SUMMARY

Enuresis is a complex problem. It may be due to psychological or organic causes, or the psychological may overlie the organic.

A greater number of enuretics than hitherto thought have an organic base for their condition.

There are two main types—obstructive and neurogenic. Obstruction causes first hypertrophy of the detrusor and sphincteric musculature; then if no infection supervenes this is followed by dilatation of the vesical neck. This dilatation may return to normal if the obstruction is removed. If the dilated sphincter does not return to normal continence can be achieved by a special plastic operation to bring about mucosal apposition by the involuntary muscle. In the presence of infection constriction at the bladder neck is likely to occur.

Early diagnosis of the cause of enuresis is essential and can, without disturbance, be achieved by the opaque cysto-urethrogram and the urethroscope. Surgical treatment offers safe and satisfactory treatment to many enuretics.

I should like to pay tribute to the willing co-operation of my medical and surgical colleagues in Belfast. I am greatly indebted to Professor Allen and his Department of Child Health for many of the patients and to Dr. Fisher, Dr. Ian Forsythe and my radiological friends for their enthusiastic help in selecting and investigating by X-ray many of these cases referred to me. I cannot speak too warmly of Dr. Ian Forsythe, who not only introduced the barium technique but helped with notes and investigations and supervision of patients. I am merely the spokesman of a co-operative effort.

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In reply to Mr. Moore and Mr. Page, who asked how many abnormalities were found in the non-persistent cases, **Mr. McFadden** said that no abnormalities were found. Since then one case with an untreated valve has been reported by the parents as being now free from enuresis.

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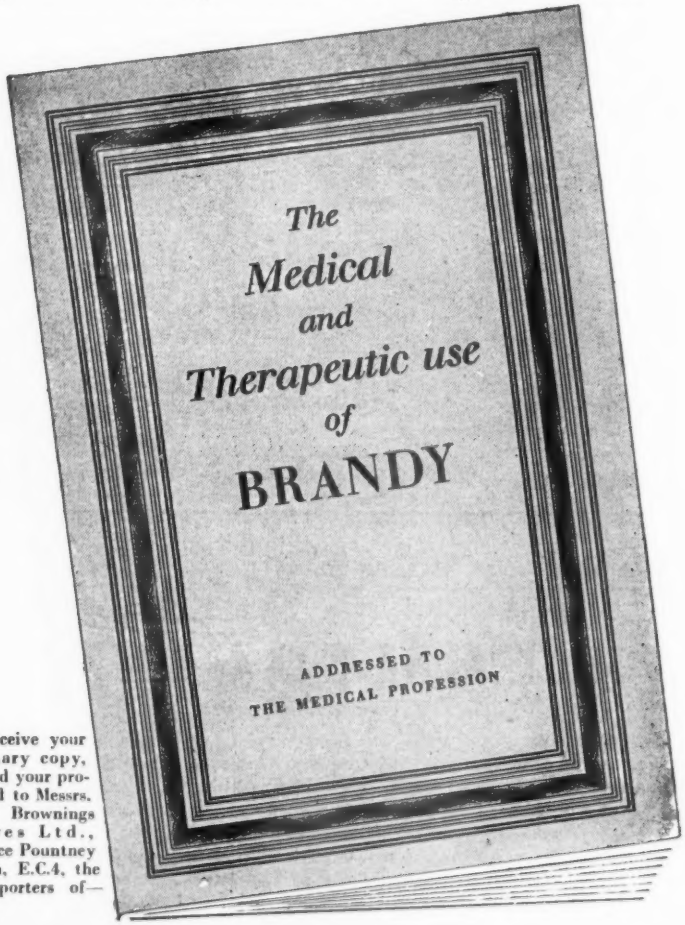

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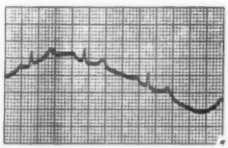

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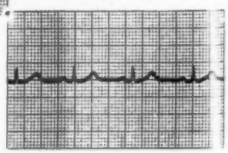

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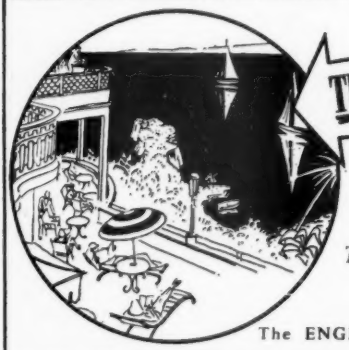

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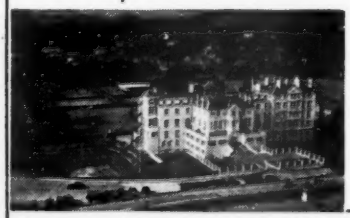

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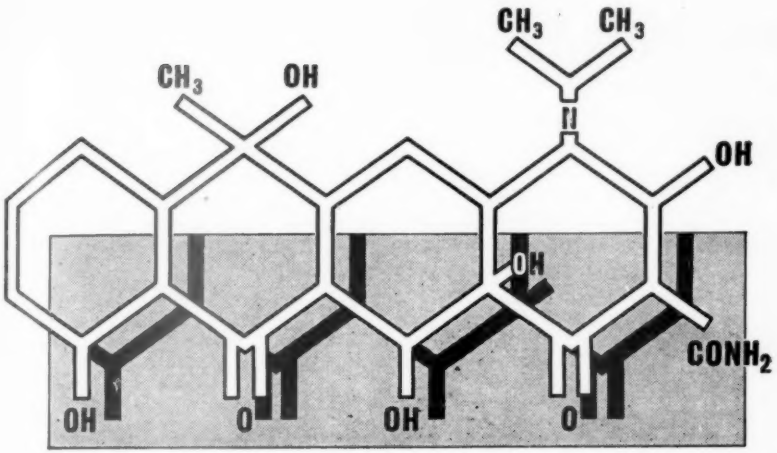

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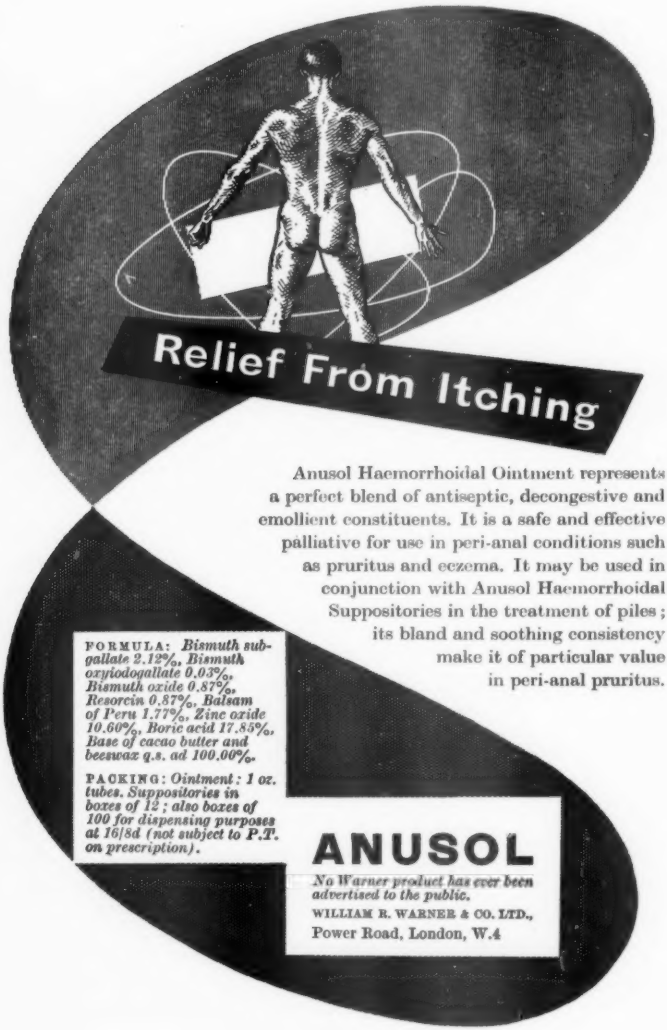

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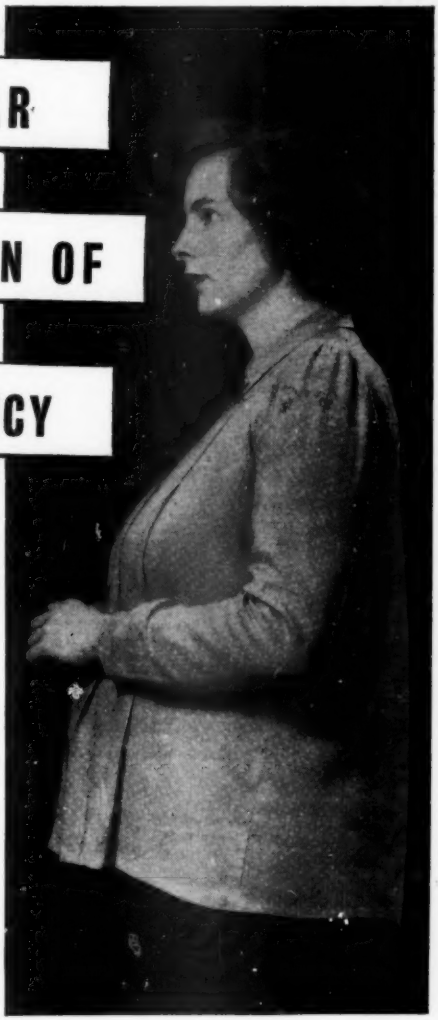

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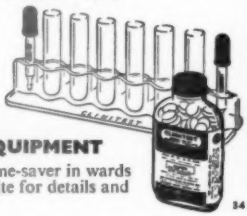

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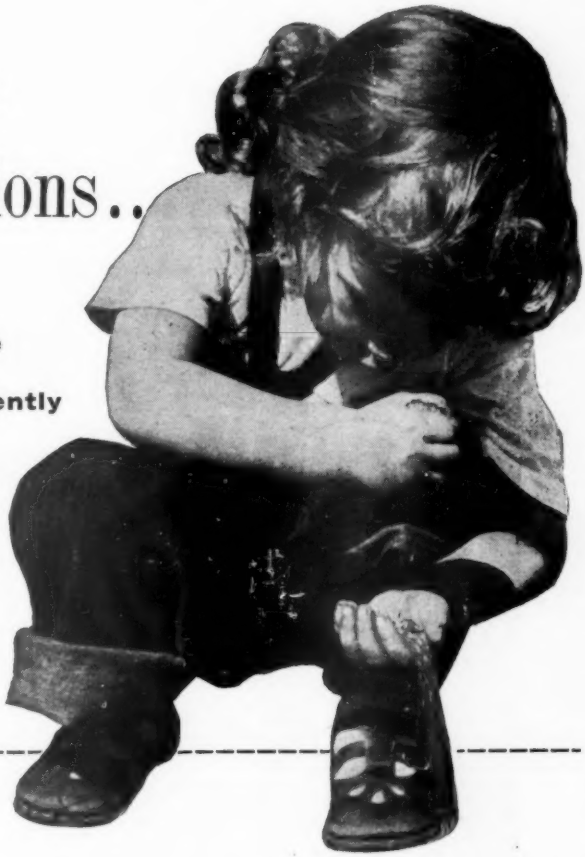

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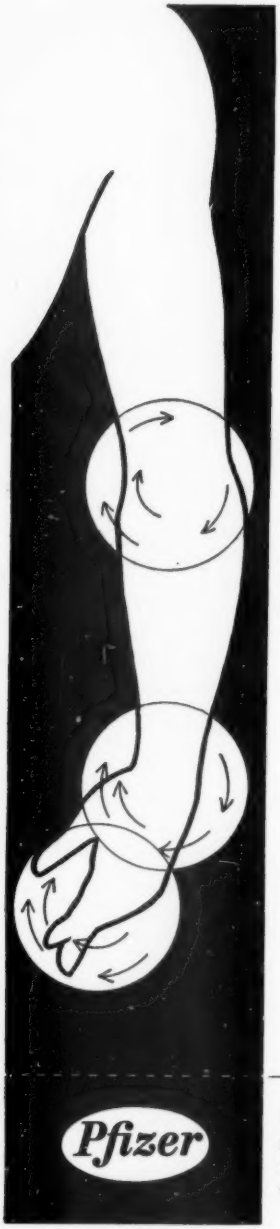

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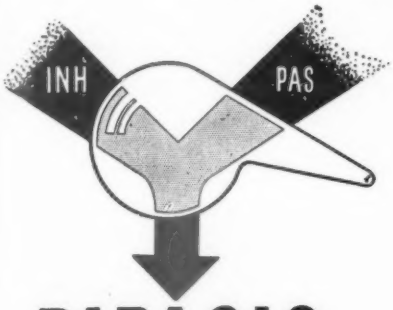

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